ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

Vol-73
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1991

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ISSN 0003-2999 Volume 73, Number 1, July 1991

For surgical procedures
90 minutes or longer...

ARDUAN

(pipecuronium bromide

for injection

Long-acting muscle relaxation without vagolytic effects[1]

- Does not cause elevation of heart rate or blood pressure.[2]
- Recommended when cardiovascular stability is desired.[3]
- A useful alternative to pancuronium in patients where tachycardia is best avoided.[4]
- Provides good to excellent intubating conditions within 2.5 to 3.0 minutes.

See following page for brief summary of prescribing information.

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(pipecuronium bromide)
for injection

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Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: None known.
WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more suitable for these patients.
PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.
Renal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.
Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.
Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.
Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.
Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermic prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.
Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate anesthesia.
Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.
Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.
Drug/Laboratory Test Interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.
Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section
Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a µg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED_{95}. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed; therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T_1 to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.
ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:
Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.
Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.
Musculoskeletal: muscle atrophy, difficult intubation.
Nervous: hypesthesia, CNS depression.
Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.
Skin and Appendages: rash, urticaria.
Urogenital System: anuria.
HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bromide. Boxes of 6 (NDC 0052-0446-36) 10 mL vials containing 10 mg lyophilized pipecuronium bromide and 10 mL vials containing bacteriostatic water for injection, USP. Boxes of 6 (NDC 0052-0446-37)
Storage: 2°-30°C (36°-86°F). Protect from light.
After Reconstitution: When reconstituted with bacteriostatic water for injection, USP: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REFERENCES

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FOR SHORTER SURGICAL PROCEDURES:
THE ALFENTA ADVANTAGE

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Rapid-acting

Alfenta®
(alfentanil HCl) Injection CII

For moment-to-moment control of stress responses

RAPID ONSET
Rapidly blocks sympathetic responses to induction and intubation

SHORT DURATION
Results in quick recovery of consciousness*

RAPID RECOVERY
Postoperative respiratory depression is of short duration*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. for

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March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

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ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

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Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1991 by the International Anesthesia Research Society. Second class postage paid at New York, NY and at additional mailing offices. Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year; in all other countries, $110.00. (See General Information in this issue for further details regarding membership.) Subscription information for 1991 applying to non-IARS members: Institutions. $140.00; nonmember individuals, $100.00. Outside the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico; $55.00 for surface airlift to Europe; $75.00 for surface airlift to Japan; and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: Anesthesia and Analgesia, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

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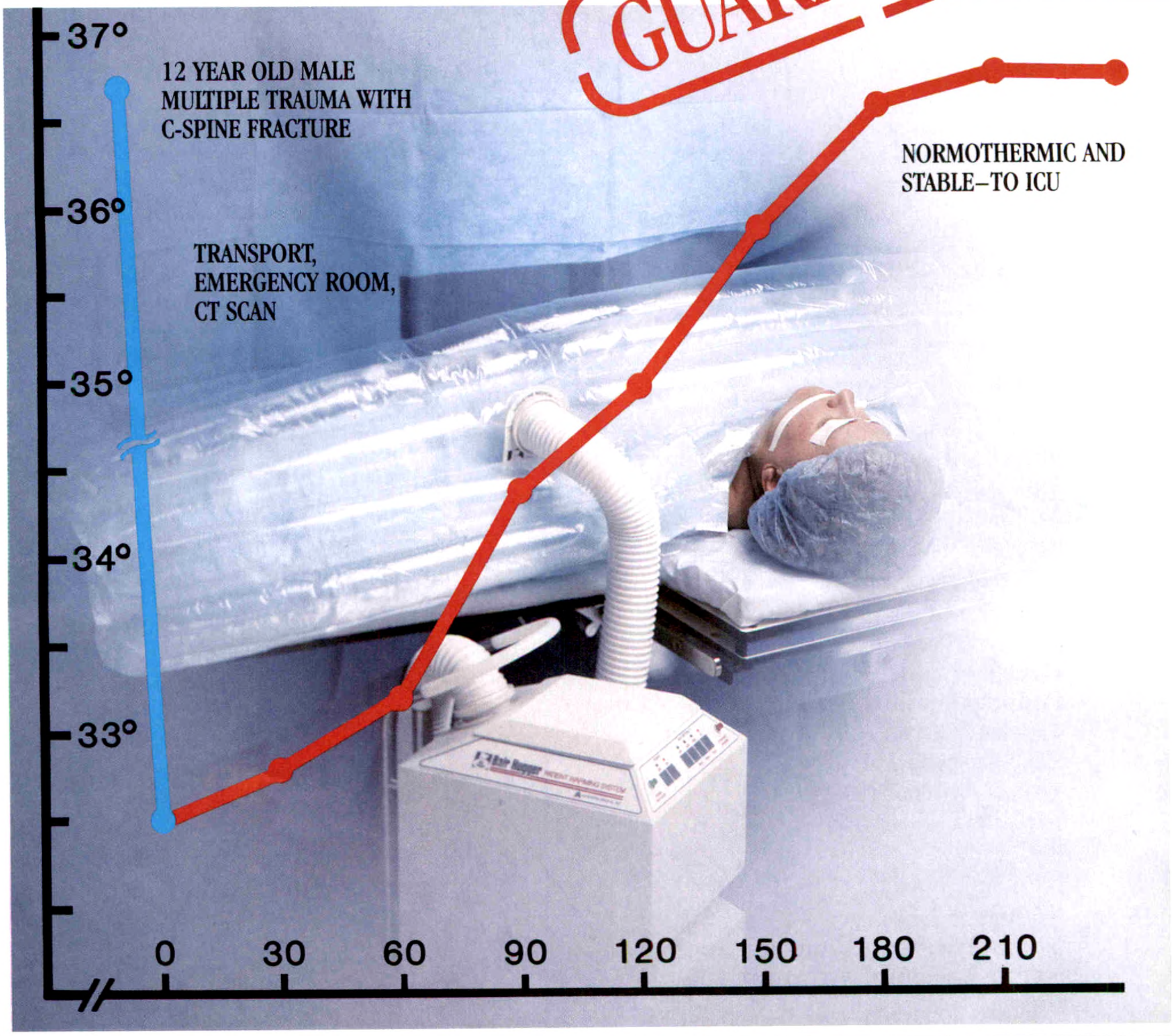

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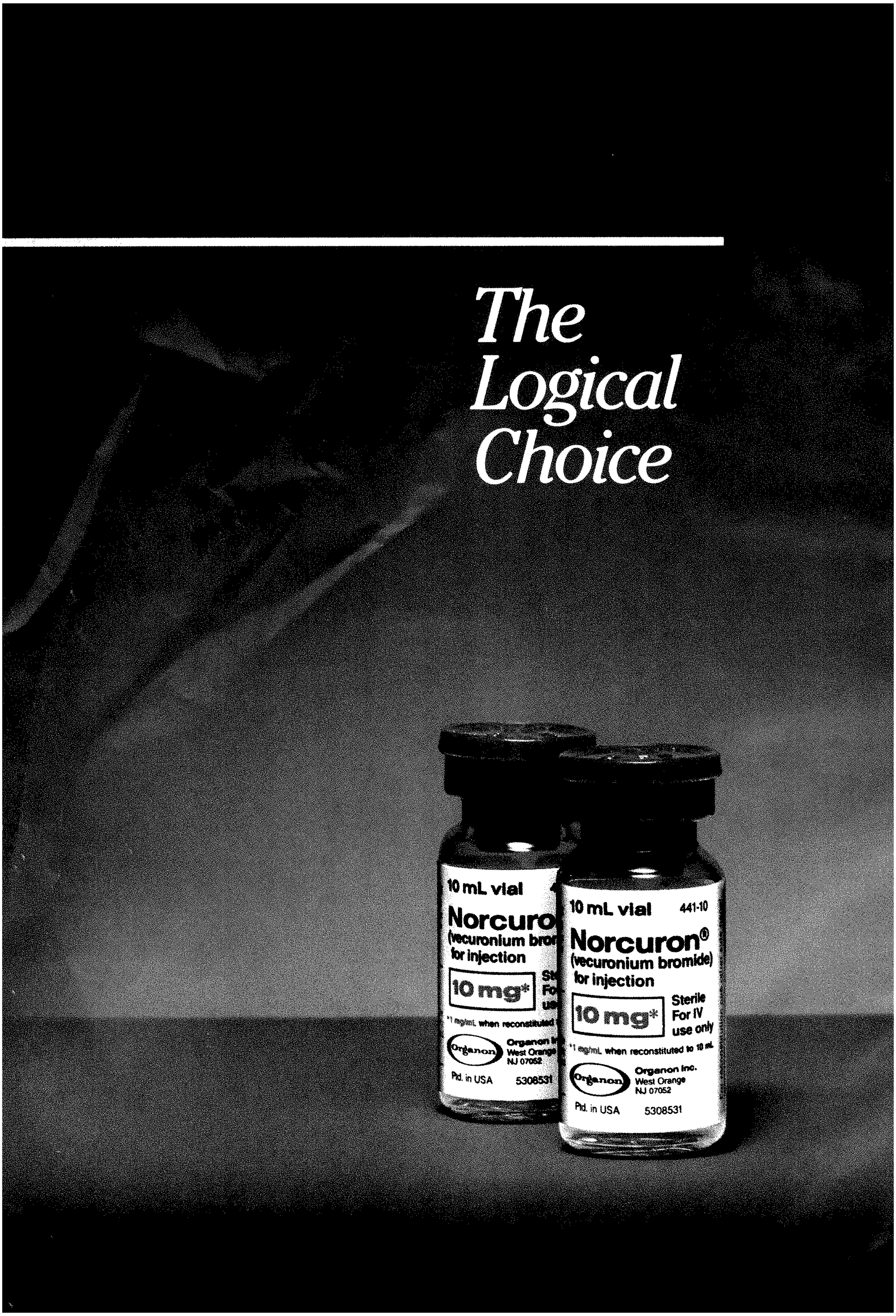
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Crucial Parameters in Selecting a Neuromuscular Blocking Agent

	Norcuron® (vecuronium bromide) for injection	**Atracurium besylate**
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance.[1]	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.[1] ($P<.05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma)[5]
RECOVERY		
To 25% of control	25–45 min[3]	35–45 min[5]
To 95% of control	45–65 min[3]	60–70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08–0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4–0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.*[2,5,7]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.† Can be reconstituted with various IV solutions including Lactated Ringers.‡	2-year shelf life under constant refrigeration.† Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

*Dose of atracurium above 0.5 mg/kg is not recommended.
†As originally supplied by the respective manufacturers.
‡Storage after reconstitution varies with solution. See package insert.

Norcuron®

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20–40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution

†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION: :

- When reconstituted with supplied bacteriostatic water for Injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for Injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

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CO-INDUCTION OF ANESTHESIA

A synergy of effects and advantages

Co-induction—when two or more agents rather than one are used for induction—may offer clinical benefits if there is anesthetic synergy. Specifically, subanesthetic doses of each agent may produce a prompt, short-acting effect with more stable hemodynamics than one agent alone.[1]

A classic example of synergy is mutual enhancement of receptor-site affinity: *e.g.,* a benzodiazepine such as VERSED may alter barbiturate receptors in a way that enhances barbiturate effects. Likewise, a barbiturate may potentiate a benzodiazepine by acting at its receptor sites.[2,3]

Lower doses of both agents

Several studies have shown that a small initial dose of VERSED will allow lower induction doses of thiopental, methohexital, fentanyl, alfentanil or ketamine.[1,4-9]

In one study of 90 unpremedicated ASA Class I & II patients, co-induction with VERSED followed by thiopental required just 1/4 of each drug's usual ED_{50}.[5]

Lower risk of breakthrough awareness

VERSED produces a marked amnestic effect. Therefore, a VERSED co-induction may reduce the possibility of recall (*e.g.,* during intubation) in the event of lightening of anesthesia with short-acting hypnotics such as thiopental or propofol.

Dosing considerations with VERSED® (midazolam HCl/Roche)Ⓒ

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.,* drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

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IDEAS IN ANESTHESIA

■ ■ ■ ■ ■ ■ ■ ■

AN ONGOING SERIES

Please see summary of product information on following page.

References: 1. Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. 2. Skolnick P, *et al.* Pentobarbital: dual actions to increase brain benzodiazepine receptor affinity. *Science.* March 1981;211:1448-1450. 3. Miller LG, *et al.* Acute barbiturate administration increases benzodiazepine receptor binding in vivo. *Psychopharmacology (Berlin).* 1988;96:385-390. 4. White PF. Comparative evaluation of intravenous agents for rapid sequence induction—thiopental, ketamine and midazolam. *Anesthesiology.* 1982;57:279-284. 5. Tverskoy M, *et al.* Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. 6. Tverskoy M, *et al.* Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth.* 1989;63:109-112. 7. Kissin I, *et al.* Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesth Analg.* 1990;71:65-69. 8. Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. 9. Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47.

VERSED®
(brand of midazolam HCl/Roche)Ⓒ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug Interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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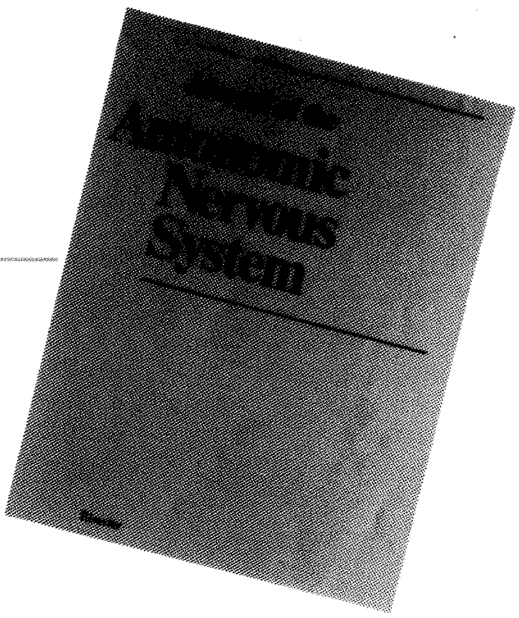

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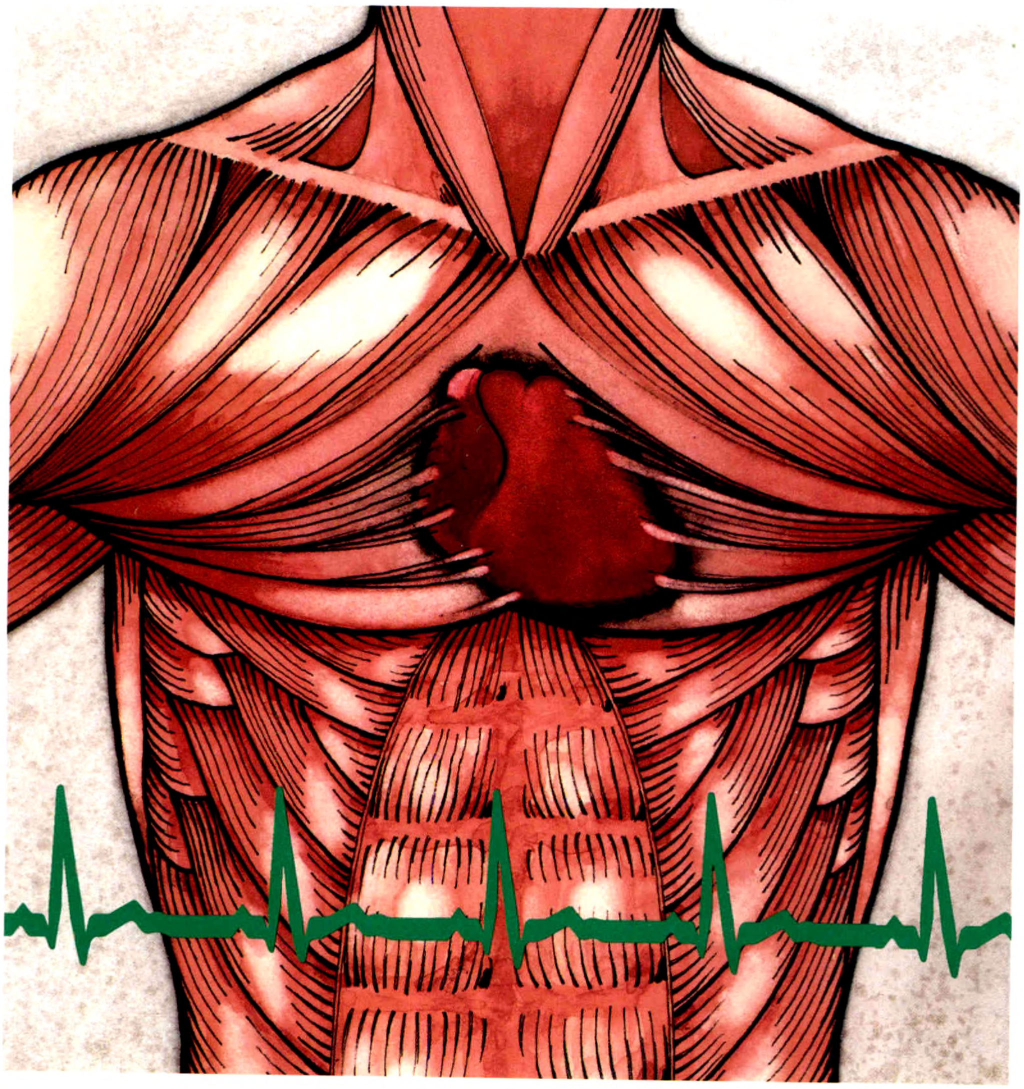
Excellent CV Stability



NUROMAX® INJECTION
(doxacurium chloride) 1 mg/mL

Please see full prescribing information on following pages.

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(doxacurium chloride)

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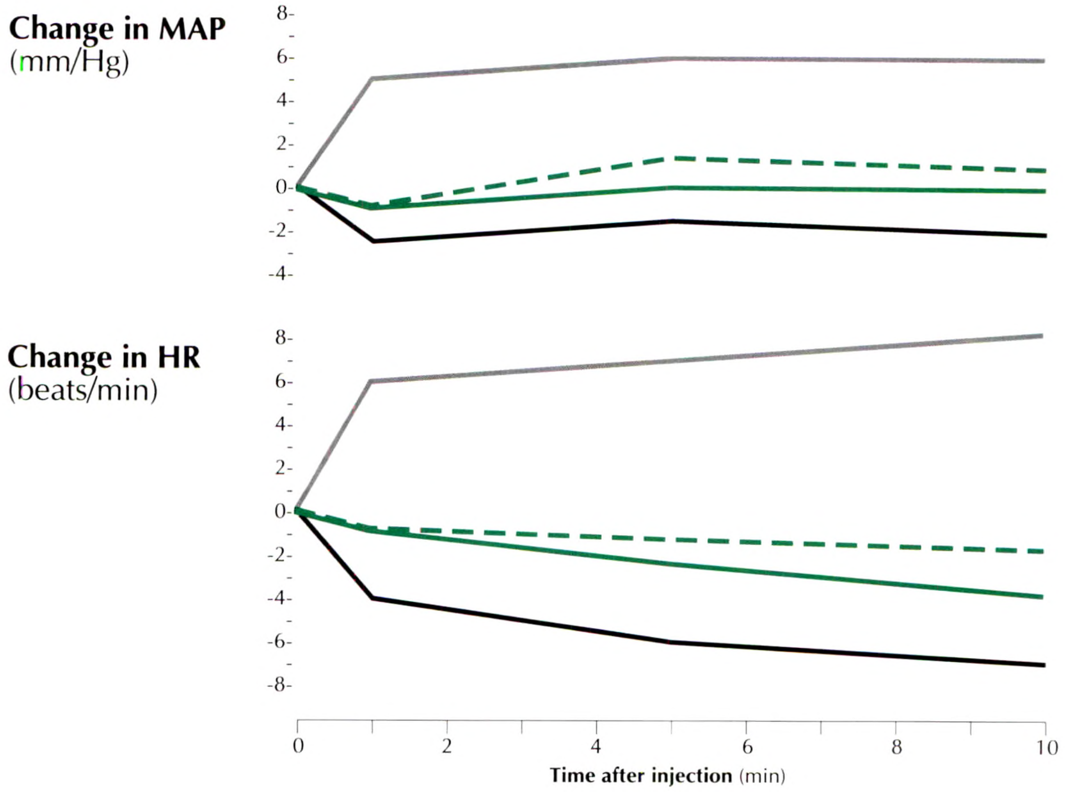
Cardiovascular stability comparable with vecuronium



Emmott et al[1] compared the hemodynamic effects of Nuromax 0.037 and 0.075 mg/kg with the effects of pancuronium 0.09 mg/kg and vecuronium 0.075mg/kg in 36 CABG patients (9 patients, each group).
Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration.
All routine cardiac and vasoactive medications were continued up to the morning of surgery.

– – doxacurium 0.037 mg/kg	▨ pancuronium 0.09 mg/kg
— doxacurium 0.075 mg/kg	— vecuronium 0.075 mg/kg

Longer acting than "high-dose" vecuronium

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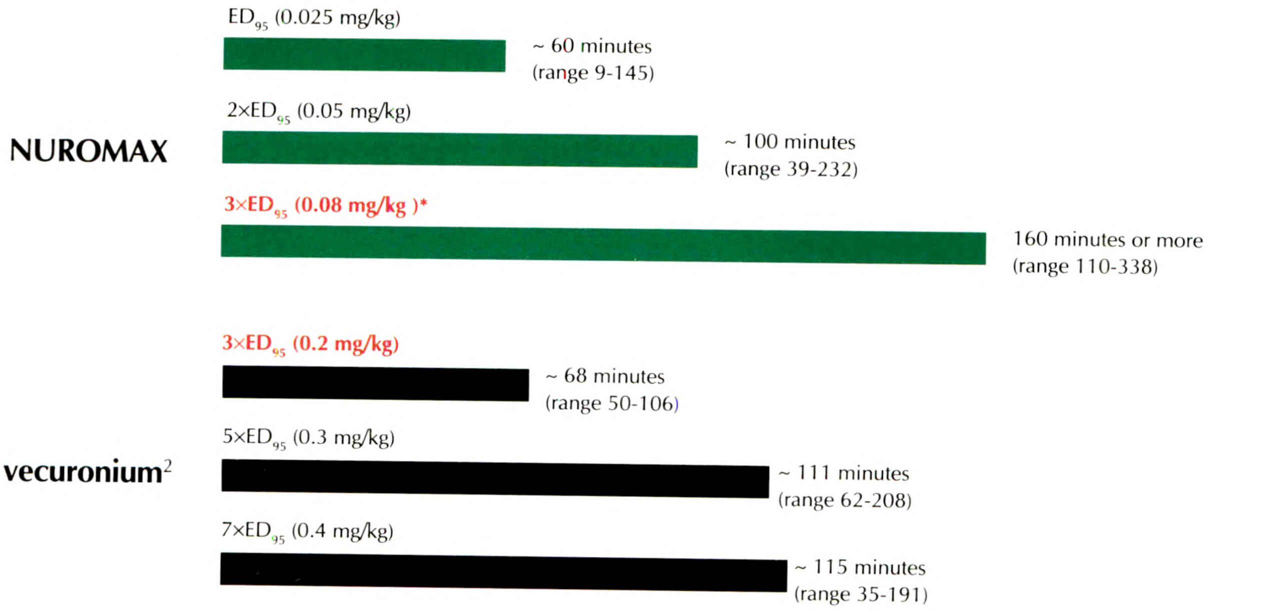
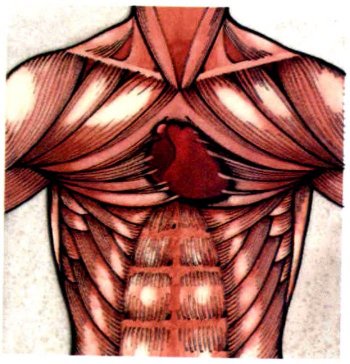


*This dose should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated.

- **Cardiovascular stability comparable with normal saline** [3]
- **Noncumulative**
- **Ready-to-use solution**
- **Vials stored at room temperature, no refrigeration required**
- **Supplied as a 5 mL vial, 1 mg/mL**



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(doxacurium chloride) 1 mg/mL

Excellent for Long CV Procedures

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NUROMAX® INJECTION
(DOXACURIUM CHLORIDE)

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Nuromax (doxacurium chloride) is a long-acting, nondepolarizing skeletal muscle relaxant for intravenous administration. Doxacurium chloride is *trans, trans*-2,2'-[succinylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride. The molecular formula is $C_{56}H_{78}Cl_2N_2O_{16}$ and the molecular weight is 1106.14. The compound does not partition into the 1-octanol phase of a distilled water/1-octanol system, *i.e.*, the n-octanol:water partition coefficient is 0.

Doxacurium chloride is a mixture of three *trans, trans* stereoisomers, a *dl* pair [(1*R*, 1'*R*, 2*S*, 2'*S*) and (1*S*, 1'*S*, 2*R*, 2'*R*)] and a meso form (1*R*, 1'*S*, 2*S*, 2'*R*).

Nuromax Injection is a sterile, non-pyrogenic aqueous solution (pH 3.9 to 5.0) containing doxacurium chloride equivalent to 1 mg/mL doxacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. Nuromax Injection contains 0.9% w/v benzyl alcohol.

CLINICAL PHARMACOLOGY: Nuromax binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.

Pharmacodynamics: Nuromax is approximately 2.5 to 3 times more potent than pancuronium and 10 to 12 times more potent than metocurine. Nuromax in doses of 1.5 to 2 x ED_{95} has a clinical duration of action (range and variability) similar to that of equipotent doses of pancuronium and metocurine (historic data and limited comparison). The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of Nuromax is 0.025 mg/kg (range: 0.020 to 0.033) in adults receiving balanced anesthesia.

The onset and clinically effective duration (time from injection to 25% recovery) of Nuromax administered alone or after succinylcholine during stable balanced anesthesia are shown in Table 1.

TABLE 1
Pharmacodynamic Dose Response* Balanced Anesthesia

	Initial Nuromax Dose (mg/kg)		
	0.025† (n=34)	0.05 (n=27)	0.08 (n=9)
Time to Maximum Block (min)	9.3 (5.4-16)	5.2 (2.5-13)	3.5 (2.4-5)
Clinical Duration (min) (Time to 25% Recovery)	55 (9-145)	100 (39-232)	160 (110-338)

* Values shown are means (range).

† Nuromax administered after 10% to 100% recovery from an intubating dose of succinylcholine.

Initial doses of 0.05 mg/kg (2 x ED_{95}) and 0.08 mg/kg (3 x ED_{95}) Nuromax administered during the induction of thiopental-narcotic anesthesia produced good-to-excellent conditions for tracheal intubation in 5 minutes (13 of 15 cases studied) and 4 minutes (8 of 9 cases studied) (which are before maximum block), respectively.

As with other long-acting agents, the clinical duration of neuromuscular block associated with Nuromax shows considerable interpatient variability. An analysis of 390 cases in U.S. clinical trials utilizing a variety of premedications, varying lengths of surgery, and various anesthetic agents, indicates that approximately two-thirds of the patients had clinical durations within 30 minutes of the duration predicted by dose (based on mg/kg actual body weight). Patients ≥ 60 years old are approximately twice as likely to experience prolonged clinical duration (30 minutes longer then predicted) than patients < 60 years old; thus, care should be used in older patients when prolonged recovery is undesirable (see **Geriatric Use** subsection of PRECAUTIONS and **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). In addition, obese patients (patients weighing ≥ 30% more than ideal body weight for height) were almost twice as likely to experience prolonged clinical duration than non-obese patients; therefore, dosing should be based on ideal body weight (IBW) for obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

The mean time for spontaneous T_1 recovery from 25% to 50% of control following initial doses of Nuromax is approximately 26 minutes (range: 7 to 104, n=253) during balanced anesthesia. The mean time for spontaneous T_1 recovery from 25% to 75% is 54 minutes (range: 14 to 184, n=184).

Most patients receiving Nuromax in clinical trials required pharmacologic reversal prior to full spontaneous recovery from neuromuscular block (see **Antagonism of Neuromuscular Block** subsection of OVERDOSAGE); therefore, relatively few data are available on the time from injection to 95% spontaneous recovery of the twitch response. As with other long-acting neuromuscular blocking agents, Nuromax may be associated with prolonged times to full spontaneous recovery. Following an initial dose of 0.025 mg/kg Nuromax, some patients may require as long as 4 hours to exhibit full spontaneous recovery.

Cumulative neuromuscular blocking effects are not associated with repeated administration of maintenance doses of Nuromax at 25% T_1 recovery. As with initial doses, however, the duration of action following maintenance doses of Nuromax may vary considerably among patients.

The Nuromax ED_{95} for children 2 to 12 years of age receiving halothane anesthesia is approximately 0.03 mg/kg. Children require higher Nuromax doses on a mg/kg basis than adults to achieve comparable levels of block. The onset time and duration of block are shorter in children than adults. During halothane anesthesia, doses of 0.03 mg/kg and 0.05 mg/kg Nuromax produce maximum block in approximately 7 and 4 minutes, respectively. The duration of clinically effective block is approximately 30 minutes after an initial dose of 0.03 mg/kg and approximately 45 minutes after 0.05 mg/kg. Nuromax has not been studied in children below the age of 2 years.

The neuromuscular block produced by Nuromax may be antagonized by anticholinesterase agents. As with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at reversal, the longer the time and the greater the dose of anticholinesterase required for recovery of neuromuscular function.

Hemodynamics: Administration of Nuromax doses up to and including 0.08 mg/kg (~3 x ED_{95}) over 5 to 15 seconds to healthy adult patients during stable state balanced anesthesia and to patients with serious cardiovascular disease undergoing coronary artery bypass grafting, cardiac valvular repair, or vascular repair produced no dose-related effects on mean arterial blood pressure (MAP) or heart rate (HR).

No dose-related changes in MAP and HR were observed following administration of up to 0.05 mg/kg Nuromax over 5 to 15 seconds in 2- to 12-year-old children receiving halothane anesthesia.

Doses of 0.03 to 0.08 mg/kg (1.2 to 3 x ED_{95}) were not associated with dose-dependent changes in mean plasma histamine concentration. Clinical experience with more than 1,000 patients indicates that adverse experiences typically associated with histamine release (*e.g.*, bronchospasm, hypotension, tachycardia, cutaneous flushing, urticaria, *etc.*) are very rare following the administration of Nuromax (see ADVERSE REACTIONS).

Pharmacokinetics: Pharmacokinetic and pharmacodynamic results from a study of 24 healthy young adult patients and 8 healthy elderly patients are summarized in Table 2. The pharmacokinetics are linear over the dosage range tested (*i.e.*, plasma concentrations are approximately proportional to dose). The pharmacokinetics of Nuromax are similar in healthy young adult and elderly patients. Some healthy elderly patients tend to be more sensitive to the neuromuscular blocking effects of Nuromax than healthy young adult patients receiving the same dose. The time to maximum block is longer in elderly patients than in young adult patients (11.2 minutes versus 7.7 minutes at 0.025 mg/kg Nuromax). In addition, the clinically effective durations of block are more variable and tend to be longer in healthy elderly patients than in healthy young adult patients receiving the same dose.

TABLE 2
Pharmacokinetic and Pharmacodynamic Parameters[1] of Nuromax in Young Adult and Elderly Patients
(Isoflurane Anesthesia)

Parameter	Healthy Young Adult Patients (22 to 49 yrs)			Healthy Elderly Patients (67 to 72 yrs)
	0.025 mg/kg (n=8)	0.05 mg/kg (n=8)	0.08 mg/kg (n=8)	0.025 mg/kg (n=8)
$t_{1/2}$ elimination (min)	86 (25-171)	123 (61-163)	98 (47-163)	96 (50-114)
Volume of Distribution at Steady State (L/kg)	0.15 (0.10-0.21)	0.24 (0.13-0.30)	0.22 (0.16-0.33)	0.22 (0.14-0.40)
Plasma Clearance (mL/min/kg)	2.22 (1.02-3.95)	2.62 (1.21-5.70)	2.53 (1.88-3.38)	2.47 (1.58-3.60)
Maximum Block (%)	97 (88-100)	100 (100-100)	100 (100-100)	96 (90-100)
Clinically Effective Duration of Block[2] (min)	68 (35-90)	91 (47-132)	177 (74-268)	97 (36-179)

1 Values shown are means (range).

2 Time from injection to 25% recovery of the control twitch height.

Table 3 summarizes the pharmacokinetic and pharmacodynamic results from a study of 9 healthy young adult patients, 8 patients with end-stage kidney disease undergoing kidney transplantation, and 7 patients with end-stage liver disease undergoing liver transplantation. The results suggest that a longer $t_{1/2}$ can be expected in patients with end-stage kidney disease; in addition, these patients may be more sensitive to the neuromuscular blocking effects of Nuromax. The time to maximum block was slightly longer and the clinically effective duration of block was prolonged in patients with end-stage kidney disease.

TABLE 3
Pharmacokinetic and Pharmacodynamic Parameters[1] of Nuromax in Healthy Patients and in Patients Undergoing Kidney or Liver Transplantation
(Isoflurane Anesthesia)

Parameter	Healthy Young Adult Patients	Kidney Transplant Patients	Liver Transplant Patients
	0.015 mg/kg (n=9)	0.015 mg/kg (n=8)	0.015 mg/kg (n=7)
$t_{1/2}$ elimination (min)	99 (48-193)	221 (84-592)	115 (69-148)
Volume of Distribution at Steady State (L/kg)	0.22 (0.11-0.43)	0.27 (0.17-0.55)	0.29 (0.17-0.35)
Plasma Clearance (mL/min/kg)	2.66 (1.35-6.66)	1.23 (0.48-2.40)	2.30 (1.96-3.05)
Maximum Block (%)	86 (59-100)	98 (95-100)	70 (0-100)
Clinically Effective Duration of Block (min)	36 (19-80)	80 (29-133)	52 (20-91)

1 Values shown are means (range).

No data are available from patients with liver disease not requiring transplantation. There are no significant alterations in the pharmacokinetics of Nuromax in liver transplant patients. Sensitivity to the neuromuscular blocking effects of Nuromax was highly variable in patients undergoing liver transplantation. Three of 7 patients developed ≤ 50% block, indicating that a reduced sensitivity to Nuromax may occur in such patients. In those patients who developed > 50% neuromuscular block, the time to maximum block and the clinically effective duration tended to be longer than in healthy young adult patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Consecutively administered maintenance doses of 0.005 mg/kg Nuromax, each given at 25% T_1 recovery following the preceding dose, do not result in a progressive increase in the plasma concentration of doxacurium or a progressive increase in the depth or duration of block produced by each dose.

Nuromax is not metabolized *in vitro* in fresh human plasma. Plasma protein binding of Nuromax is approximately 30% in human plasma.

In vivo data from humans suggest that Nuromax is not metabolized and that the major elimination pathway is excretion of unchanged drug in urine and bile. In studies of healthy adult patients, 24% to 38% of an administered dose was recovered as parent drug in urine over 6 to 12 hours after dosing. High bile concentrations of Nuromax (relative to plasma) have been found 35 to 90 minutes after administration. The overall extent of biliary excretion is unknown. The data derived from analysis of human urine and bile are consistent with data from *in vivo* studies in the rat, cat, and dog, which indicate that all of an administered dose of Nuromax is recovered as parent drug in the urine and bile of these species.

Individualization of Dosages: In elderly patients or patients who have impaired renal function, the potential for a prolongation of block may be reduced by decreasing the initial Nuromax dose and by titrating the dose to achieve the desired depth of block. In obese patients (patients weighing ≥ 30% more than ideal body weight for height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2

Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Dosage requirements for patients with severe liver disease are variable; some patients may require a higher than normal initial Nuromax dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged in such patients relative to patients with normal liver function.

As with pancuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity and/or shortened duration of block, must be considered when Nuromax is selected for use in patients receiving phenytoin or carbamazepine (see **Drug Interactions** subsection of PRECAUTIONS).

As with other nondepolarizing neuromuscular blocking agents, a reduction in dosage of Nuromax must be considered in cachectic or debilitated patients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or carcinomatosis, and in other patients in whom potentiation of neuromuscular block or difficulty with reversal is anticipated. Increased doses of Nuromax may be required in burn patients (see PRECAUTIONS).

INDICATIONS AND USAGE: Nuromax is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia, to provide skeletal muscle relaxation during surgery. Nuromax can also be used to provide skeletal muscle relaxation for endotracheal intubation.

CONTRAINDICATIONS: Nuromax is contraindicated in patients known to have hypersensitivity to it.

WARNINGS: NUROMAX SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS NUROMAX EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANTS, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM.

NUROMAX HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Nuromax Injection is acidic (pH 3.9 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Nuromax Injection contains benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. See **Pediatric Use** subsection of PRECAUTIONS.

PRECAUTIONS: General: Nuromax has no clinically significant effects on heart rate; therefore, Nuromax will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a small test dose of Nuromax is recommended to assess the level of neuromuscular block and to monitor dosage requirements. Shorter acting muscle relaxants than Nuromax may be more suitable for these patients.

Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns depending upon the time elapsed since the injury and the size of the burn. Nuromax has not been studied in patients with burns.

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Nuromax has not been studied in patients with asthma.

No data are available to support the use of Nuromax by intramuscular injection.

Renal and Hepatic Disease: Nuromax has been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing transplantation procedures (see CLINICAL PHARMACOLOGY). The possibility of prolonged neuromuscular block in patients undergoing renal transplantation and the possibility of a variable onset and duration of neuromuscular block in patients undergoing liver transplantation must be considered when Nuromax is used in such patients.

Obesity: Administration of Nuromax on the basis of actual body weight is associated with a prolonged duration of action in obese patients (patients weighing ≥ 30% more than ideal body weight for height) (see CLINICAL PHARMACOLOGY). Therefore, the dose of Nuromax should be based upon ideal body weight in obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-susceptible patients. Since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of Nuromax in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of Nuromax.

The use of Nuromax before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on concomitant use of Nuromax and other nondepolarizing neuromuscular blocking agents.

Isoflurane, enflurane and halothane decrease the ED_{50} of Nuromax by 30% to 45%. These agents may also prolong the clinically effective duration of action by up to 25%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Nuromax include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine.

As with some other nondepolarizing neuromuscular blocking agents, the time of onset of neuromuscular block induced by Nuromax is lengthened and the duration of block is shortened in patients receiving phenytoin or carbamazepine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Nuromax was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, in the mouse lymphoma assay, and in the human lymphocyte assay. In the *in vivo* rat bone marrow cytogenetic assay, statistically significant increases in the incidence of structural abnormalities, relative to vehicle controls, were observed in male rats dosed with 0.1 mg/kg (0.625 mg/m^2) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in female rats dosed with 0.2 mg/kg (1.25 mg/m^2) Nuromax and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female rats given 0.3 mg/kg (1.875 mg/m^2) Nuromax and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic assay was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is low.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Teratology testing in nonventilated, pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of Nuromax revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Nuromax in pregnant women. Because animal studies are not always predictive of human response and the doses used were subparalyzing, Nuromax should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of Nuromax during labor, vaginal delivery, or cesarean section has not been studied. It is not known whether Nuromax administered to the mother has immediate or delayed effects on the fetus. The duration of action of Nuromax exceeds the usual duration of operative obstetrics (cesarean section). Therefore, Nuromax is not recommended for use in patients undergoing C-section.

Nursing Mothers: It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following Nuromax administration to a nursing woman.

Pediatric Use: Nuromax has not been studied in children below the age of 2 years. See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age.

Geriatric Use: Nuromax has been used in elderly patients, including patients with significant cardiovascular disease. In elderly patients the onset of maximum block is slower and the duration of neuromuscular block produced by Nuromax is more variable and, in some cases, longer than in young adult patients (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: The most frequent adverse effect of nondepolarizing blocking agents as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesia. This effect may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency and apnea which require manual or mechanical ventilation until recovery is judged to be clinically adequate (see OVERDOSAGE). Inadequate reversal of neuromuscular block from Nuromax is possible, as with all nondepolarizing agents. Prolonged neuromuscular block and inadequate reversal may lead to postoperative complications.

Observed in Clinical Trials: Adverse experiences were uncommon among the 1034 surgical patients and volunteers who received Nuromax and other drugs in U.S. clinical studies in the course of a wide variety of procedures conducted during balanced or inhalational anesthesia. The following adverse experiences were reported in patients administered Nuromax (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater than 1% - None

Incidence Less than 1% -

Cardiovascular*:	hypotension,† flushing,† ventricular fibrillation, myocardial infarction
Respiratory:	bronchospasm, wheezing
Dermatological:	urticaria, injection site reaction
Special Senses:	diplopia
Nonspecific:	difficult neuromuscular block reversal, prolonged drug effect, fever

* Reports of ventricular fibrillation (n=1) and myocardial infarction (n=1) were limited to ASA Class 3-4 patients undergoing cardiac surgery (n=142).

† 0.3% incidence. All other reactions unmarked were ≤ 0.1%.

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent (see **Antagonism of Neuromuscular Block**).

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCK. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED. T_4/T_1 SHOULD BE > ZERO BEFORE ANTAGONISM IS ATTEMPTED.

In an analysis of patients in whom antagonism of neuromuscular block was evaluated following administration of single doses of neostigmine averaging 0.06 mg/kg (range: 0.05 to 0.075) administered at approximately 25% T_1 spontaneous recovery during balanced anesthesia, 71% of patients exhibited $T_4/T_1 \geq 0.7$ before monitoring was discontinued. For these patients, the mean time to $T_4/T_1 \geq 0.7$ was 19 minutes (range: 7 to 55). As with other long-acting nondepolarizing neuromuscular blocking agents, the time for recovery of neuromuscular function following administration of neostigmine is dependent upon the level of residual neuromuscular block at the time of attempted reversal; longer recovery times than those cited above may be anticipated when neostigmine is administered at more profound levels of block (*i.e.*, at < 25% T_1 recovery).

Patients should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of Nuromax on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., < 60% T_1 recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block. The use of pyridostigmine has not been studied.

DOSAGE AND ADMINISTRATION: NUROMAX SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

Nuromax, like other long-acting neuromuscular blocking agents, displays variability in the duration of its effect. The potential for a prolonged clinical duration of neuromuscular block must be considered when Nuromax is selected for administration. The dosage information provided below is intended as a guide only. Doses should be individualized (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include: advancing age, the presence of kidney or liver disease, or obesity (patients weighing ≥ 30% more than ideal body weight for height). The use of a peripheral nerve stimulator will permit the most advantageous use of Nuromax, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Adults: ***Initial Doses:*** When administered as a component of a thiopental/narcotic induction-intubation paradigm as well as for production of long-duration neuromuscular block during surgery, 0.05 mg/kg (2 x ED_{95}) Nuromax produces good-to-excellent conditions for tracheal intubation in 5 minutes in approximately 90% of patients. Lower doses of Nuromax may result in a longer time for development of satisfactory intubation conditions. Clinically effective neuromuscular block may be expected to last approximately 100 minutes on average (range: 39 to 232) following 0.05 mg/kg Nuromax administered to patients receiving balanced anesthesia.

An initial Nuromax dose of 0.08 mg/kg (3 x ED_{95}) should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated. In approximately 90% of patients, good-to-excellent intubation conditions may be expected in 4 minutes after this dose; however, clinically effective block may be expected to persist for as long as 160 minutes or more (range: 110 to 338) (see CLINICAL PHARMACOLOGY).

If Nuromax is administered during steady-state isoflurane, enflurane, or halothane anesthesia, reduction of the Nuromax dose by one-third should be considered.

When succinylcholine is administered to facilitate tracheal intubation in patients receiving balanced anesthesia, an initial dose of 0.025 mg/kg (ED_{95}) Nuromax provides about 60 minutes (range: 9 to 145) of clinically effective neuromuscular block for surgery. For a longer duration of action, a larger initial dose may be administered.

Maintenance Doses: Maintenance dosing will generally be required about 60 minutes after an initial dose of 0.025 mg/kg Nuromax or 100 minutes after an initial dose of 0.05 mg/kg Nuromax during balanced anesthesia. Repeated maintenance doses administered at 25% T_1 recovery may be expected to be required at relatively regular intervals in each patient. The interval may vary considerably between patients. Maintenance doses of 0.005 and 0.01 mg/kg Nuromax each provide an average 30 minutes (range: 9 to 57) and 45 minutes (range: 14 to 108), respectively, of additional clinically effective neuromuscular block. For shorter or longer desired durations, smaller or larger maintenance doses may be administered.

Children: When administered during halothane anesthesia, an initial dose of 0.03 mg/kg (ED_{95}) produces maximum neuromuscular block in about 7 minutes (range: 5 to 11) and clinically effective block for an average of 30 minutes (range: 12 to 54). Under halothane anesthesia, 0.05 mg/kg produces maximum block in about 4 minutes (range: 2 to 10) and clinically effective block for 45 minutes (range: 30 to 80). Maintenance doses are generally required more frequently in children than in adults. Because of the potentiating effect of halothane seen in adults, a higher dose of Nuromax may be required in children receiving balanced anesthesia than in children receiving halothane anesthesia to achieve a comparable onset and duration of neuromuscular block. Nuromax has not been studied in children below the age of 2 years.

Compatibility: ***Y-site Administration:*** Nuromax Injection may not be compatible with alkaline solutions with a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Nuromax is compatible with:

- 5% Dextrose Injection USP
- 0.9% Sodium Chloride Injection USP
- 5% Dextrose and 0.9% Sodium Chloride Injection USP
- Lactated Ringer's Injection USP
- 5% Dextrose and Lactated Ringer's Injection
- Sufenta® (sufentanil citrate) Injection, diluted as directed
- Alfenta® (alfentanil hydrochloride) Injection, diluted as directed
- Sublimaze® (fentanyl citrate) Injection, diluted as directed

Dilution Stability: Nuromax diluted up to 1:10 in 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP has been shown to be physically and chemically stable when stored in polypropylene syringes at 5° to 25°C (41° to 77°F), for up to 24 hours. Since dilution diminishes the preservative effectiveness of benzyl alcohol, aseptic techniques should be used to prepare the diluted product. Immediate use of the diluted product is preferred, and any unused portion of diluted Nuromax should be discarded after 8 hours..

HOW SUPPLIED: Nuromax Injection, 1 mg doxacurium in each mL.

5 mL Multiple Dose vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS). Tray of 10 (NDC 0081-0763-44).

STORAGE: Store Nuromax Injection at room temperature of 15° to 25°C (59° to 77°F). DO NOT FREEZE.

U.S. Patent No. 4701460

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3. Stoops CM, Curtis CA, Kovach DA, et al. Hemodynamic effects of doxacurium chloride in patients receiving oxygen sufentanil anesthesia for coronary artery bypass grafting or valve replacement. *Anesthesiology.* 1988;69:365-370.

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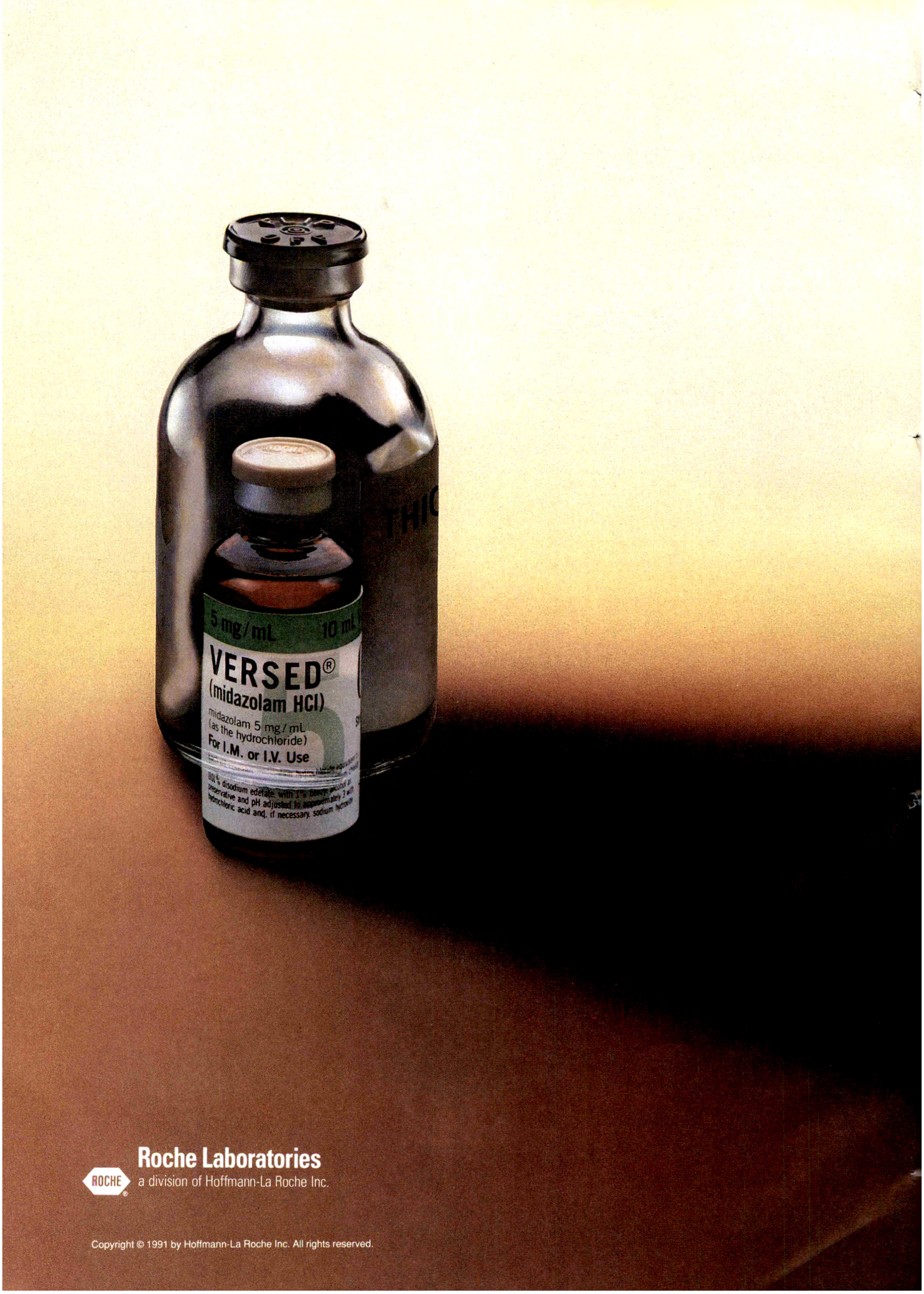
5 mg/mL
10 mL
VERSED®
(midazolam HCl)
midazolam 5 mg/mL
(as the hydrochloride)
For I.M. or I.V. Use
disodium edetate, with 1% benzyl alcohol as
preservative and pH adjusted to approximately 3 with
hydrochloric acid and, if necessary, sodium hydroxide
THI

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THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED_{50} of barbiturates or narcotics up to 75%.[1-4] This synergistic effect appears to result from a mutual enhancement of binding-site affinity.[1-3] Clinically, co-induction may decrease toxicity and speed recovery.[2] VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,[5] and its potent amnestic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- **Allows lower doses of induction agents[1-5]**
- **A smooth induction[5,6]**
- **Less risk of breakthrough awareness[5,6]**
- **A smooth emergence[5,6]**

Dosing considerations

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

Please see summary of product information on following page.

INJECTABLE

VERSED®

midazolam HCl/Roche Ⓒ

FIRST

Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

References: 1. Tverskoy M, *et al*. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. **2.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. **3.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. **4.** Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47. **5.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology.* 1982;57:279-284. **6.** Desiderio DP, Thorne AC. Awareness and general anaesthesia. *Acta Anaesthesiol Scand.* 1990;34(suppl 92):48-50.

VERSED®
(brand of midazolam HCl/Roche)Ⓒ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED.

Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

VERSED® (brand of midazolam HCl/Roche)

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1991 AWARDS

At the IARS 65th Congress in March 1991, the Board of Trustees announced recipients of the 1991 Award as follows:

Mitchell F. Berman, MD, Columbia University, New York, NY:
"Blockade of Cardiac Sodium Channels by Local Anesthetics. Whole-Cell and Single-Channel Analysis"
Alberto J. de Armendi, MD, AM, Massachusetts General Hospital, Boston, MA:
"Mechanisms of Anaesthesia of Volatile and Barbiturate Anaesthetics at the Acetylcholine Receptor"
Stephen W. King, PhD, MD, University of California, San Francisco:
"Anesthetic Effects on the Inositol Triphosphate Receptor"
Pontus Ostman, MD, The University of Iowa, Iowa City, IA:
"The Efficacy and Hemodynamic Effects of Epidurally Administered Dexmedetomidine Towards Visceral and Thermal Nociceptive Stimulus in the Gravid Guinea Pig"
Mark S. Scheller, MD, University of California, San Diego:
"Modifications of Patterns of Hippocampal Excitatory Amino Acid Concentrations Following Global Cerebral Ischemia in Rabbits by Two Voltage Dependent Calcium Channel Antagonists"
Margaret M. Sedensky, MD, Case Western Reserve University, Cleveland, OH:
"Analysis of the Site(s) of Action of Volatile Anesthetics by Molecular Genetics"

1992 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1992 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than December 13, 1991. Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
2 Summit Park Dr., #140
Cleveland, OH 44131
Telephone: (216) 642-1124

The 1992 Award(s) will be announced at the Annual Scientific Meeting (66th Congress) of the International Anesthesia Research Society to be held at the San Francisco Hilton & Towers, March 13–17, 1992.

Mock Orals Help Dr. Smith

Home-study, lectures, and practice oral exams – limited to 90 participants

The *Osler Institute* Anesthesiology Boards Tutorial

July 6-11, 1991 – Chicago August 9-12, 1991 – Atlanta
August 15-19, 1991 – Chicago August 23-26, 1991 – Los Angeles
September 30-October 5 – Tampa

Dear Fellow Physician:

Dr. Smith (not his real name) had failed his oral boards several times. His group was satisfied with his work but his job depended on becoming board certified. He was eligible to take the exam only one more time. A friend advised him to take our Osler Institute's Anesthesiology Board Review Course.

Home Study Questions

Before the course, we sent him several hundred pages of multiple choice questions with answers as well as keywords with explanations. These were given to us by past participants. Now we also have a collection of mock-oral-exam stem cases and related questions to send you.

Free Sample Offer

We offer to send you a gift without obligation: a free sample of our multiple choice questions or our mock oral cases. We would like to share these with you whether or not you take our course. Please request on course registration form.

Complete Syllabus

We can also send you a copy of a previous course syllabus. Our price to you is $60 (about our production cost). The supply is limited. Those registering for the six day lecture course will receive several hundred pages of current lecture notes and all home study materials at no extra charge.

Great Lectures

At the course, Dr. Smith enjoyed six days of outstanding lectures by some of the best-known teachers in anesthesiology – as well as by several outstanding junior faculty who had been asked back because of their excellent participant evaluation scores. Also several new faculty had been recommended for their speaking ability.

Some of the lectures were of little use to Dr. Smith – he is regarded as an expert in his field; he could have given several of the lectures himself. Knowledge was not his problem; his problem was presenting his knowledge in the oral exam. He skipped several lectures to attend:

Mock Oral Exams

The first day of the course, a recently retired board examiner explained the philosophy, process, and scoring of the real oral exam. Each evening as well as concurrent with most lectures there were mock oral exams for Dr. Smith. These are group sessions with one participant taking the hot seat for about 25 minutes while others watch. Each participant is entitled to a turn in the hot seat as well as unlimited observation of others.

When Dr. Smith took the hot seat his heart quickened, his palms sweated, and his hands shook. The faculty presented a stem question, paused a minute, then asked the first question. Dr. Smith opened his mouth, but his tongue was thick and dry. He stammered and stuttered – failed to form even a sentence – just like when he failed the real oral exam. But this time was different; the faculty coached and encouraged him. His panic passed and his performance improved.

Extra Mock Orals

The course budget could not support enough faculty for an unlimited number of mock orals for every participant. In our previous course, assertive attendees had taken the hot seat repeatedly before others had a chance. In response, we mark participant name tags for the first mock oral. We also hire additional faculty time and sell $70 tickets for extra turns in the hot seat.

Dr. Smith became more comfortable in the hot seat. He continued to improve.

Private and Dual Orals

Dr. Lee, however, was too shy to take the hot seat in front of anyone else. We now have a thirty dollar surcharge for private sessions. Also, Dr. Jones wanted two examiners, just like the real exam. Such sessions take twice the faculty time, so we must charge $140 per session.

Video Mock Orals

At our June course, we had a portable TV studio to make educational tapes with some of the faculty. Video taping mock orals was so popular that we now offer a video tape of your practice exam for an extra ten dollars per session.

Extra Mock Oral Days

Lectures end on Saturday and the real oral exams are the next Monday through Friday. What do you do in the meantime? Sunday through Tuesday of oral exam week are optional extra days of mock oral exams. For $140 per day, attendees receive one 25 minute hot seat session and observation of other sessions for nine hours.

Your Individual Needs

The quality of our courses gave us growth. Growth helped us improve to meet your individual needs. At the course, you may choose every hour between a lecture or observation of one-on-one mock oral exams.

Passing Your Boards

Will our course help you pass your boards? Dr. Smith passed his oral exam the week after our course. A candidate calling to register for our course told us:

> *"Five of my partners took your course; they all passed their oral boards; and they all recommended your course."*

One of our faculty reported:

> *"All of my residents who took the course passed their boards."*

We can't guarantee that you will pass. We can't say that taking our course will make the difference between passing or failing. All we can say is that a lot of our participants tell us that the course was helpful. See registration form to request a free sample.

We look forward to meeting you at our course and helping you to pass your board exams.

Cordially,

Joe Selliken

Joseph H. Selliken, Jr., M.D.

P.S. To reserve your place call today

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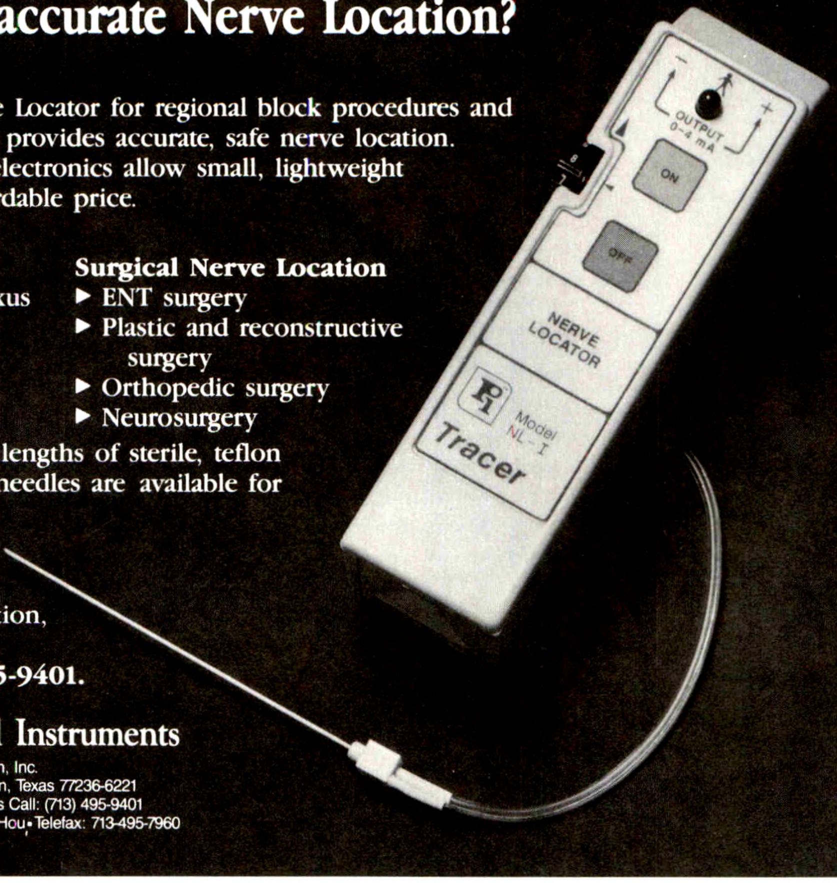

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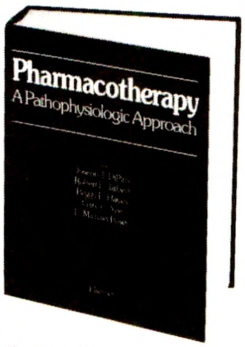

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The *International Journal of Cardiology* is devoted to cardiology in the broadest sense. Both basic research and clinical papers may be submitted, but articles on the fundamental principles of cardiology will also be considered for publication. The journal serves the interest of both practicing clinicians and research workers. Editorials, Brief Reports and Review Articles covering recent developments are included. Controversial techniques, issues on Health Policy and Social Medicine are discussed and serve as useful tools for encouraging debate.

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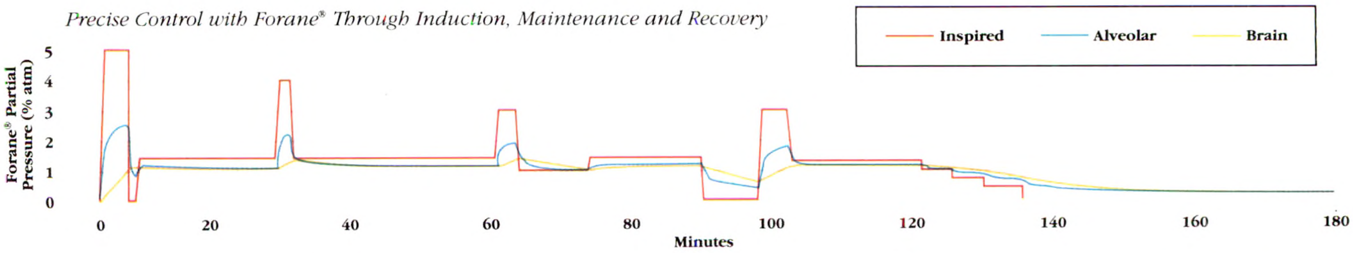

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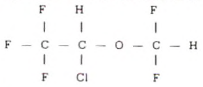

$$\mathrm{F-\overset{F}{\underset{F}{C}}-\overset{H}{\underset{Cl}{C}}-O-\overset{F}{\underset{F}{C}}-H}$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where:} \quad A = 8.056,\ B = -1664.58,\ T = {}^\circ C + 273.16\ (\text{Kelvin})$$

Partition coefficients at 37 °C		
Water/gas		0.61
Blood/gas		1.43
Oil/gas		90.8
Partition coefficients at 25 °C - rubber and plastic		
Conductive rubber/gas		62.0
Butyl rubber/gas		75.0
Polyvinyl chloride/gas		110.0
Polyethylene/gas		~2.0
Polyurethane/gas		~1.4
Polyolefin/gas		~1.1
Butyl acetate/gas		~2.5
Purity by gas chromatography		>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °	None	
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °	Greater than useful concentration in anesthesia.	

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Isoflurane can produce coronary vasodilation at the arteriolar level in selected animal models[1,2]; the drug is probably also a coronary dilator in humans. Isoflurane, like some other coronary arteriolar dilators, has been shown to divert blood from collateral dependent myocardium to normally perfused areas in an animal model ("coronary steal")[3]. Clinical studies to date evaluating myocardial ischemia, infarction and death as outcome parameters have not established that the coronary arteriolar dilation property of isoflurane is associated with coronary steal or myocardial ischemia in patients with coronary artery disease[4,5,6,7].

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Regardless of the anesthetics employed, maintenance of normal hemodynamics is important to the avoidance of myocardial ischemia in patients with coronary artery disease[4,5,6,7].

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken.

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane,

b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\,P_V\,F_V}{F_T\,(P_A - P_V)}$$

where:
P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature 15 ° - 30 °C (59 ° - 86 °F). Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

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EDITORIAL

The Changing of the Guard

Ronald D. Miller, MD, Editor-in-Chief

During his 14 years as editor-in-chief, Nicholas M. Greene, MD, transformed *Anesthesia and Analgesia* into a legitimate, first-rate scientific journal in the field of anesthesiology. The International Anesthesia Research Society (IARS) should be congratulated for having selected Dr. Greene as their editor-in-chief and for giving him the support necessary to make this transformation possible. Dr. Greene restructured the editorial board so that it was composed of editors who were academically qualified to provide valid critiques of manuscripts submitted for publication, and he emphasized the search for original and significant papers. Although he succeeded in attracting many important manuscripts, he expressed frustration in his 1991 address to the IARS that the proliferation of scientific journals was allowing a larger number of manuscripts to be published that were insignificant or irrelevant. This trend, he noted, makes it increasingly difficult to identify manuscripts of true worth. Despite his frustration with this general trend in scientific publishing, Dr. Greene consistently demanded quality in the manuscripts to be published in *Anesthesia and Analgesia*. For members of the journal's editorial board, Dr. Greene's stewardship amounted to a continuing education course in how to identify and assess quality manuscripts and in more general matters related to the role of journals within the academic and scientific community. Although Dr. Greene insisted upon excellence in the writing and science of work submitted for publication, his critiques of manuscripts were remarkably gentle and encouraging. In fact he is often described as the only editor-in-chief who could make an author feel good about having a manuscript rejected. Gradually, under Dr. Greene's care, the journal's subscriptions and advertising increased, allowing the IARS to develop a substantial research support program which by 1992 will have granted more than $1,000,000 to young and aspiring investigators in anesthesiology.

The challenge for the journal's "new guard" is to protect the quality of *Anesthesia and Analgesia* which Dr. Greene labored so diligently to develop and, at the same time, to sustain its reputation as a leader in the field. Our primary task in meeting this challenge is to ensure that we are responding to the changing nature of anesthesiology—a field that has become increasingly subspecialized. The practitioner who can provide anesthesia for all types of surgery—critical care as well as pain management—is rapidly becoming extinct. In response to this trend, the editorial board of *Anesthesia and Analgesia* has itself been partially subdivided, reflecting the seven major subspecialties of our discipline. Manuscripts submitted for publication that involve one of those subspecialties will be reviewed by subspecialists, and the management of the review process in these cases will be conducted, for the most part, by an appropriate section editor rather than by the editor-in-chief. For example, manuscripts involving pediatrics or ambulatory surgery will have their reviews managed by Dr. Paul Hickey or Dr. Patricia Kapur, respectively. The philosophy reflected here—that decisions regarding manuscripts involving a subspecialty should be made by the scientific leaders of that subspecialty—is responsible for one of the major changes in the editorial management of *Anesthesia and Analgesia*. Although this new approach will add some degree of complexity, we are confident that newer techniques, such as electronic communications and computerized database management, will help to ensure that the review process remains rapid and efficient.

As Dr. Greene's criticisms of recent trends in scientific publishing imply, the quality of any journal can only be as good as the quality of the manuscripts it receives. With this in mind, one important change that must be addressed by the "new guard" is the fact that many advances in basic and clinical anesthesiology, and therefore many of the best manuscripts, have been contributed by the international anesthesia community. Accordingly, to continue to attract a high quality of manuscripts from this community, and to maintain a global perspective in the evaluation of such manuscripts, the composition of the editorial board of *Anesthesia and Analgesia* will itself become increasingly international. We already have an advantage in having as editorial board members Dr. Nimmo and Dr. Bevan (from Scotland and Canada, respectively), and we are now delighted to announce the addition of Dr. Mori from Japan and Dr. Van Aken from Belgium. In addition, we have added some depth to our editorial office staff to assist those

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authors whose first language is not English. We believe that these developments will be a major step forward in creating a truly international editorial capability for *Anesthesia and Analgesia.*

Finally, we hope that the readership of the journal will recognize that the achievements of *Anesthesia and Analgesia* to date rest largely on the support that the editorial board has received from the IARS. The charge of the IARS has been to produce the best basic and clinical scientific journal possible. In working to meet that charge, the "new guard" and the current editorial board will strive to protect the accomplishments gained under Dr. Greene's leadership and to meet the new challenges of the 1990s.

CARDIOVASCULAR ANESTHESIA
Section Editor
Joseph G. Reves

Left Ventricular Performance During Propofol or Methohexital Anesthesia: Isotopic and Invasive Cardiac Monitoring

Jean-Yves M. Lepage, MD, Michel L. Pinaud, MD, PhD, Jacques H. Helias, MD, Antoine Y. Cozian, MD, Yves Le Normand, PharmD, and Remy J. Souron, MD

Département d'Anesthésie-Réanimation Chirurgicale and Service de Médecine Nucléaire, Centre Hospitalier Régional et Universitaire, Nantes, France; Laboratoire de Pharmacologie, Faculté de Médecine, Nantes, France

Using gated radionuclide ventriculography and invasive cardiac monitoring, the effects of propofol and methohexital on left ventricular volumes and function were investigated in 22 unpremedicated patients (ASA physical status III, 50–78 yr) with chronic coronary artery disease (NYHA class II-III). Anesthesia was induced with either propofol or methohexital (2 mg/kg), followed by a maintenance infusion of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Vecuronium (0.05 mg/kg) was administered and ventilation ($\mathrm{FIO_2}$, 1.0) was manually controlled ($\mathrm{FECO_2}$, 0.04–0.05). Data acquisitions were serially obtained over 15 min. Propofol and methohexital anesthesia caused an average 15% decrease in mean arterial pressure, associated with a 20% decrease in cardiac index without a decrease in systemic vascular resistance index. It is interesting that the determinants of these hemodynamic effects were different. Heart rate did not change during propofol infusion despite the decrease in mean arterial pressure, whereas heart rate increased during methohexital infusion. In the propofol group, the decrease in cardiac index was associated with decreases in indicators of preload (end-diastolic volume and pulmonary capillary wedge pressure), whereas end-systolic volume and global ejection fraction did not change statistically. In the methohexital group, the decrease in cardiac index was associated with a decrease in global ejection fraction and an increase in end-systolic volume, whereas indicators of preload remained unchanged. It is concluded that methohexital reduces left ventricular performance. In contrast, propofol preserves left ventricular performance despite a likely negative inotropic effect.

(Anesth Analg 1991;73:3–9)

Propofol and methohexital are short-acting intravenous anesthetics with pharmacokinetic properties that make them suitable for maintenance of anesthesia by continuous intravenous infusion (1,2). Propofol seems to be more depressant to the cardiovascular system than are the IV barbiturate-induction agents (3–5). Reported effects of propofol on the cardiovascular system are conflicting. They can be considered, however, to be the result of both vasodilation and negative inotropic effect (which are responsible for arterial hypotension and decreased stroke volume) (5–8). During high-dose methohexital anesthesia sufficient to produce electroencephalographic suppression, vasodilation and some depressed myocardial function also have been reported (9). There are, nevertheless, no data establishing the left ventricular volumes during methohexital anesthesia and contrasting the determinants of the hemodynamic effects of propofol and methohexital under comparable conditions. The present report discusses the effects on left ventricular performance of propofol or methohexital as the sole anesthetic in patients with stable chronic coronary artery disease using gated radionuclide ventriculography and invasive cardiac monitoring.

Methods

Patients

Twenty-two ASA physical status III patients undergoing major urologic surgery were randomly (10) assigned to two groups of 11 patients each to receive either methohexital or propofol. All patients had angina pectoris (NYHA class II-III) secondary to

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Supported in part by the University of Nantes Institutional Grants Program.

Presented in part at the annual meeting of the International Anesthesia Research Society, Lake Buena Vista, Florida, March 1989.

Accepted for publication February 20, 1991.

Address correspondence to Dr. Lepage, Département d'Anesthésie, CHRU, Hôtel-Dieu, B.P. 1005, 44035 Nantes Cedex 01, France.

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0003-2999/91/$3.50

coronary artery disease but none had congestive heart failure, valvular heart disease, hypertension, or previous myocardial infarction, nor was any patient being treated with β-blocking agents. The diagnosis of coronary artery disease was established by the presence of typical angina pectoris brought on by effort and relieved by rest and nitroglycerin, and further documented by positive exercise tests (ST segment horizontal depression or downsloping greater than or equal to 0.1 mV). Premedication was not used, but usual anginal medications (nifedipine and isosorbide) were continued preoperatively up to the time of the procedure. The study, approved by our local ethics committee, was performed in the nuclear medicine laboratory just before surgery. Informed written consent was obtained in each case.

Invasive Monitoring

Two 18-gauge catheters were placed into two forearm veins for administration of drugs and radionuclide-labeled red blood cells. A 7.5F thermodilution Swan Ganz catheter (93A-831-7.5F, American Edwards Laboratories) was percutaneously inserted into the pulmonary artery via an antecubital or internal jugular vein for measurement of pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output. A 20-gauge cannula was placed into a nondominant radial artery for monitoring arterial blood pressure and for blood sampling. Approximately 10 mL of 1% lidocaine was used subcutaneously during catheter insertion in all patients. Heart rate was measured from leads II and V_5 of the electrocardiogram. Pressures and electrocardiogram were continuously displayed on a monitor and recorded on a polygraph. Thermodilution measurements of cardiac output were made with iced injectate in triplicate within 1.5 min and expressed as the mean value. All cardiac output, pulmonary artery pressure, and pulmonary capillary wedge pressure measurements were made at the end of expiration. Derived variables including cardiac index, stroke index, and systemic vascular resistance index were calculated using standard formulas (11) after the completion of the study. Systemic and mixed venous blood samples were simultaneously withdrawn within 1 min after cardiac output measurements. Oxygen partial pressure, $P\text{CO}_2$, pH, hemoglobin concentration, and hemoglobin saturation ($S\text{aO}_2$ and $S\text{vO}_2$) were measured with an ABL 300 Radiometer. Arterial and mixed venous oxygen content, arteriovenous difference in oxygen contents, indexed oxygen consumption, and oxygen extraction ratio were calculated using standard formulas (12).

Isotopic Study

All patients were studied by radionuclide angiography using first-pass and electrocardiographic gated equilibrium blood-pool techniques with in vivo ^{99m}Tc-labeled red blood cells. The basic principle of this technique is that radioactivity recorded from the left ventricle in a left anterior oblique view is proportional to left ventricular volumes after correction for absorption of radiation in the myocardium and the thoracic wall using an attenuation factor. The technique has been extensively described previously (7). Thirty minutes after stannous pyrophosphate (TCK 7 CEA) pretreatment, a first-pass study was done following the intravenous injection of 2 mCi of ^{99m}Tc-pertechnetate (Technetium CEA Elumat 300), making possible the measurement of isotopic cardiac output using the Stewart Hamilton principle and the estimation of the attenuation factor. A 20-mCi source was then injected and an equilibrium study was performed: left ventricular regions of interest were drawn on end-diastolic and end-systolic images; mean end-diastolic and end-systolic counts, left ventricular end-diastolic and end-systolic areas, and global ejection fraction were calculated for 1.5 min; exact numerical values in milliliters of end-diastolic volume, end-systolic volume, stroke volume, and densitometric cardiac output were obtained using the attenuation factor. Densitometric cardiac output and first-pass isotopic dilution cardiac output were compared in each patient for validation of the method. The necessary time for each isotopic acquisition was fixed at 1.5 min to be contemporaneous with the hemodynamic study.

Protocol

A baseline set of hemodynamic and densitometric isotopic measurements (awake) was recorded before anesthetic induction. Anesthesia was then induced with either propofol or methohexital (2 mg/kg in 20 s), followed by an infusion of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Vecuronium (0.05 mg/kg) was administered and ventilation ($F\text{IO}_2$, 1.0) was manually controlled to maintain $F\text{ECO}_2$ between 0.04 and 0.05 (47210 A Capnometer, Hewlett Packard). Six series of measurements, including hemodynamic and densitometric isotopic data, were then made between 1 and 2.5 (T1), 3 and 4.5 (T3), 6 and 7.5 (T6), 9 and 10.5 (T9), 12 and 13.5 (T12), and 15 and 16.5 min (T15). Arterial and mixed venous blood samples were obtained at baseline, T3, T6, and T15 for blood gas analysis. Arterial blood samples were obtained at each recorded point for measurement of propofol or methohexital concentrations. After the last of the data acquisitions described above, the trachea was intubated and the patient was moved into the operating room.

Determination of Propofol and Methohexital Concentrations

Samples for propofol determination were placed into tubes that contained potassium oxalate and then stored at 4°C before analysis. Whole blood propofol concentrations were measured after extraction into cyclohexane by a high-pressure liquid chromatographic method using fluorescence detection (13). The limit of sensitivity of the assay to propofol is approximately 2 ng/mL, and the coefficient of variation over the concentration range measured is approximately 8%. Samples for methohexital determination were placed into tubes that contained lithium heparin. After immediate centrifugation of blood samples, plasma was separated and stored at −18°C until analyzed. The methohexital plasma concentrations were measured after extraction into chloroform by gas chromatography using capillary column and nitrogen-selective detection (14). The limit of sensitivity of the assay to methohexital is 6 ng/mL and intraassay variability is 5.5%.

Table 1. Patient Characteristics

	Propofol group (n = 11)	Methohexital group (n = 11)
Age (yr)	68 (50–76)	69 (51–78)
Weight (kg)	68 (55–83)	67 (52–85)
Height (cm)	170 (153–189)	173 (158–183)
Angina pectoris		
NYHA II (n)	5	6
NYHA III (n)	6	5
Treatment		
Nifedipine (n)	6	5
Isosorbide (n)	10	9

NYHA, New York Heart Association classification system.

Values for age, weight, and height are expressed as the mean, with the range given in parentheses.

There were no significant differences between groups.

Data Analysis

Student's t-test and one-factor analysis of variance with repeated measurements were used for statistical analy-

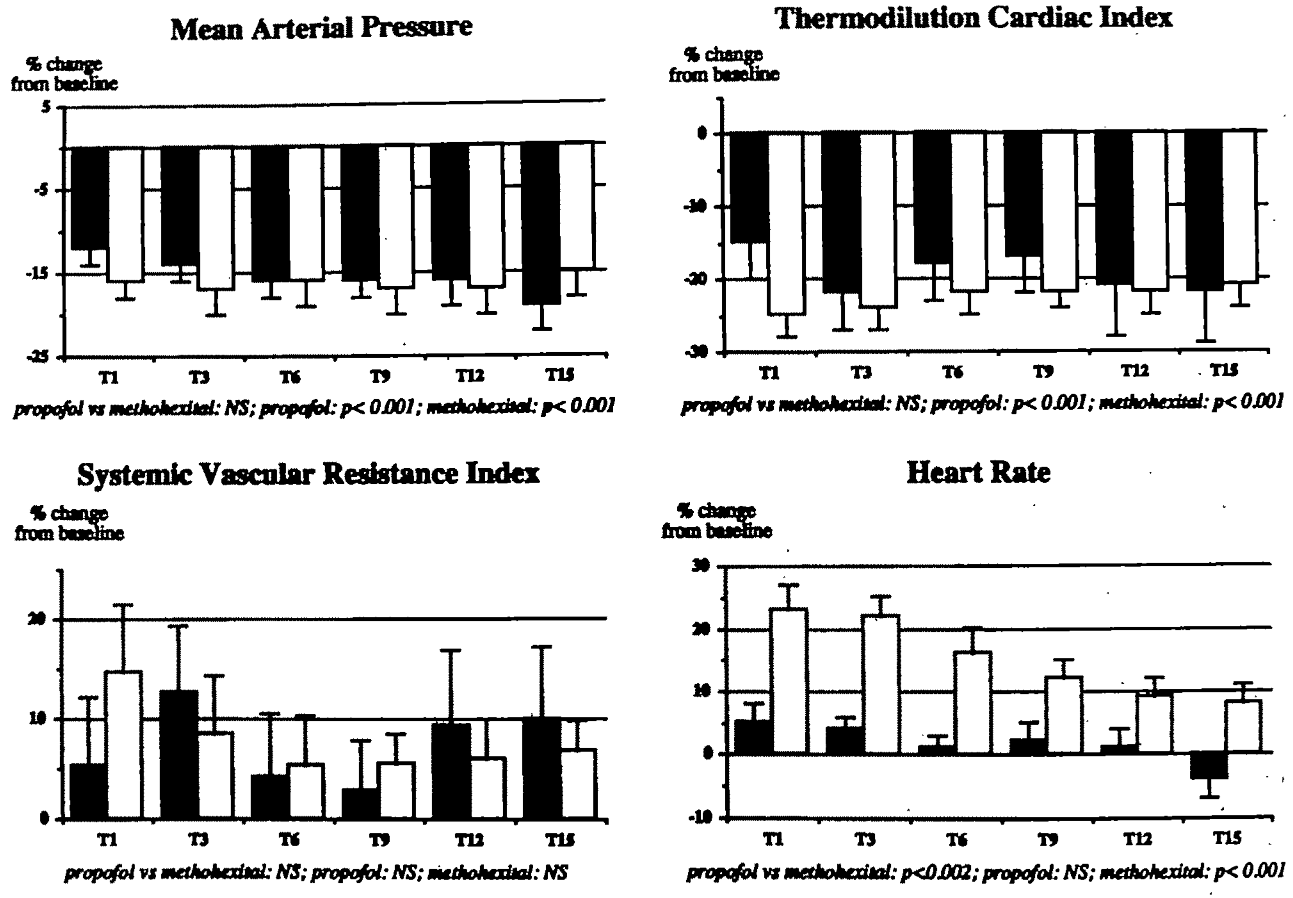

Figure 1. Mean arterial pressure, thermodilution cardiac index, systemic vascular resistance index, and heart rate changes associated with propofol (*solid bars*) and methohexital (*open bars*) anesthesia, expressed in percent change from baseline values (mean ± SEM).

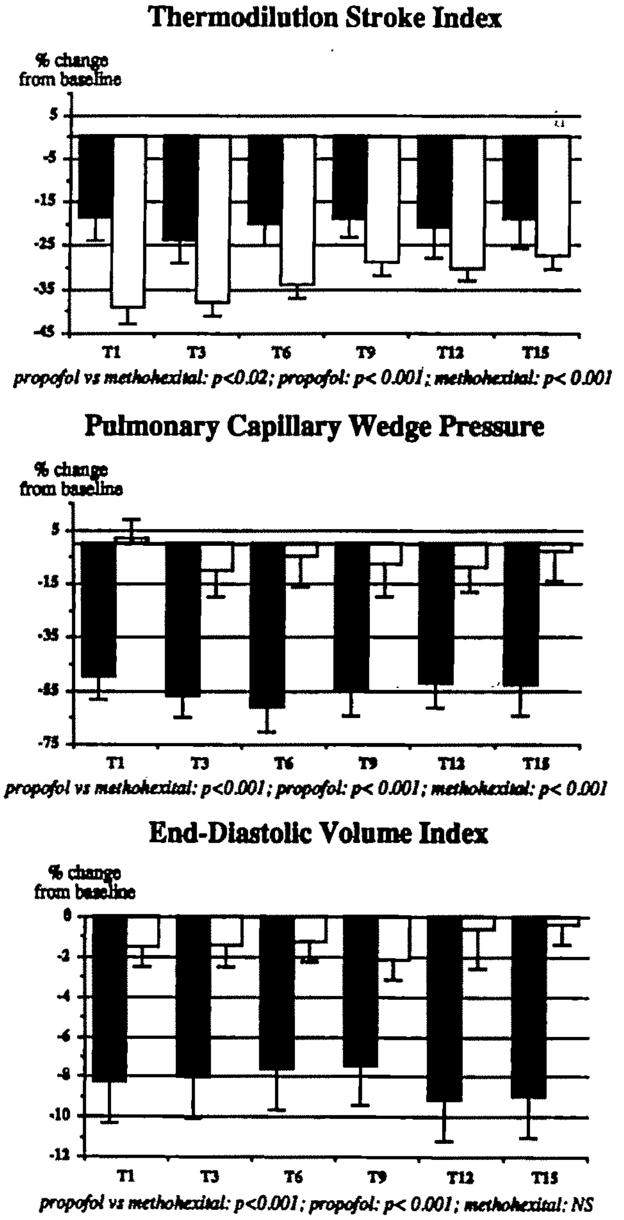

Figure 2. Thermodilution stroke index, pulmonary capillary wedge pressure, and end-diastolic volume index changes associated with propofol (*solid bars*) and methohexital (*open bars*) anesthesia, expressed in percent change from baseline values (mean ± SEM).

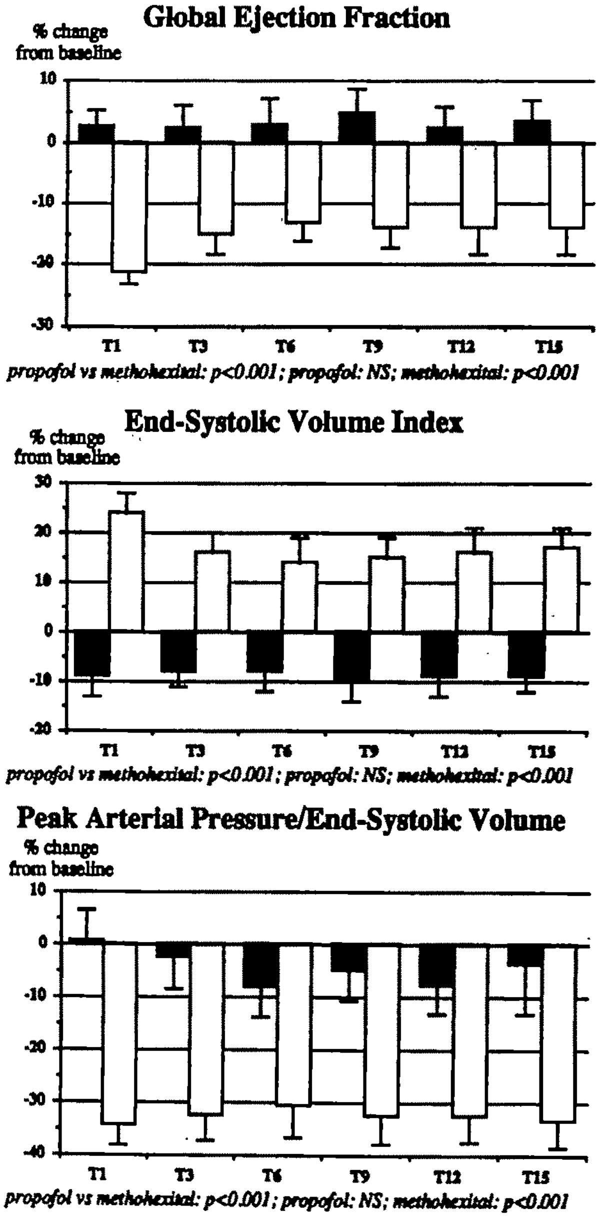

Figure 3. Global ejection fraction, end-systolic volume index changes, and peak arterial blood pressure/end-systolic volume ratio changes associated with propofol (*solid bars*) and methohexital (*open bars*) anesthesia, expressed in percent change from baseline values (mean ± SEM).

sis. Correlations between specific variables were tested for significance with a linear regression method. Statistical significance was accepted at $P < 0.05$.

Results

The two groups were similar with regard to age, weight, height, NYHA class of coronary artery disease, and treatment (Table 1). The most important results are presented in Figures 1–3 and Tables 2 and 3. There were no significant differences in baseline values between the two groups. The administration of either propofol or methohexital followed by a maintenance infusion caused an average 15% decrease in mean arterial pressure. This was associated with a 20% decrease in cardiac index without a decrease in systemic vascular resistance index. Heart rate did not change during propofol infusion despite the decrease in mean arterial pressure, whereas heart rate increased during methohexital infusion. In the

Table 2. Awake Hemodynamics Data

	Propofol group	Methohexital group
HR (beats/min)	71 ± 4	74 ± 3
MAP (mm Hg)	99 ± 5	101 ± 5
PCWP (mm Hg)	6.1 ± 0.6	6 ± 0.6
thCI ($\mathrm{L \cdot min^{-1} \cdot m^{-2}}$)	3.14 ± 0.2	2.96 ± 0.2
thSI ($\mathrm{mL \cdot beat^{-1} \cdot m^{-2}}$)	45.1 ± 2.3	41.2 ± 2.8
SVRI ($\mathrm{dyne \cdot s \cdot cm^{-5} \cdot m^{-2}}$)	2480 ± 125	2732 ± 202
EF (%)	55.7 ± 1.7	54.4 ± 1.8
EDVI ($\mathrm{mL/m^2}$)	81.2 ± 3.6	77.2 ± 3.6
ESVI ($\mathrm{mL/m^2}$)	35.2 ± 1.9	34.4 ± 1.9

All values are expressed as mean ± SEM.

HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; thCI, thermodilution cardiac index; thSI, thermodilution stroke index; SVRI, systemic vascular resistance index; EF, ejection fraction; EDVI, end-diastolic volume index; ESVI, end-systolic volume index.

There were no significant differences between groups.

propofol group, the decrease in cardiac index was associated with decreases in indicators of preload (end-diastolic volume, pulmonary capillary wedge pressure). The average 9% decrease in end-systolic volume and the average 3% increase in ejection fraction were not statistically significant. When compared with propofol, methohexital anesthesia resulted in lowered cardiac index associated with a significant 15% decrease in ejection fraction and a 17% increase in end-systolic volume, whereas indicators of preload remained unchanged. In both groups, indexed oxygen consumption decreased 50%, accompanied by a decrease in arteriovenous difference in oxygen contents and oxygen extraction ratio. There was a significant linear relationship between densitometric cardiac output and first-pass isotopic cardiac output ($y = 0.896x + 0.513$; $n = 22$; $r = 0.976$; $P < 0.0001$). There was a significant relationship between stroke index measured by the thermodilution technique and isotopic densitometric stroke index ($y = 0.633x + 15.506$; $n = 152$; $r = 0.679$; $P < 0.001$). No ST segment changes (>0.1 mV), no auricular or ventricular ectopic beats, and no conduction abnormalities occurred during the entire procedure. Whole blood propofol and plasma methohexital concentrations are displayed in Figure 4. Both drugs reached a plateau close to pharmacologic steady state and a clinically stable depth of anesthesia was achieved.

Discussion

Before discussing the results of the present study it should be noted that to allow comparison of the features of hemodynamic responses to intravenous infusions of anesthetics, it has been suggested that the minimal infusion rate—the rate that would suppress movement in response to the initial surgical incision in 50% of the patients (MIR ED$_{50}$)—be used as an index of equipotency comparable to the minimal alveolar concentration (MAC) for volatile anesthetics (15). In the present study, an infusion rate of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which is double the MIR ED$_{50}$ of both propofol (16) and methohexital (17), provided adequate anesthetic blood concentrations (1,18). In addition, the circulatory changes associated with intravenous anesthesia are related for the most part to conditions of vascular tone before the injection. Our patients took their cardiac medication (nifedipine and isosorbide) up to the morning of the study, and this may have influenced hemodynamic responses.

Our findings confirm that both propofol and methohexital have cardiovascular depressant effects. These include a mean 15% decrease in mean arterial pressure associated with a mean reduction in cardiac index of 20%, and a maximum decrease in stroke index of 25% with propofol and 40% with methohexital. Both drugs caused a 50% decrease in oxygen consumption with a simultaneous reduction in arteriovenous difference in oxygen contents and oxygen extraction ratio, suggesting a decrease in oxygen demand, which in turn probably contributed to the decrease in cardiac index.

Heart rate did not change during propofol anesthesia whereas it increased during methohexital anesthesia. Normally, arterial baroreceptors regulate arterial pressure by modifying heart rate and systemic vascular resistances. Samain et al. (19) and Cullen et al. (20) demonstrated that propofol does not impair the baroreflex sensitivity but instead resets the baroreflex control allowing a lower level of arterial pressure for a given heart rate and/or systemic vascular resistances. The effect of methohexital on baroreflex control has been shown to be different (21): the sensitivity of the baroreflex is markedly decreased, but the response is reset to allow a more rapid heart rate at lower arterial pressure than when awake. An inhibition of central vagal activity is involved.

The effect of propofol anesthesia on baroreflex activity suggests a direct vasodilating action of propofol on vascular smooth muscle associated with a central depression of sympathetic outflow or a central vagotonic predominance (or both) (20). We did not find a decrease in the calculated systemic vascular resistances, but the fact that resistances did not increase despite the decrease in cardiac index indicates a certain degree of arterial vasodilation. This vasodilation also results in an increase in venous capacitance as reflected in the simultaneous decreases in stroke index and preload indicators. Whether propofol-induced vasodilation involves mainly the arteries rather than the venous capacitance is still controver-

Table 3. Blood Gas and Derived Data Associated with Propofol and Methohexital

	Drug	Awake	T3	T6	T15	P^a
Vo_2I (mL $O_2 \cdot min^{-1} \cdot m^{-2}$)	P	94 ± 9.4	46 ± 3.9	49 ± 2.5	49 ± 3.0	<0.001
	M	102 ± 5.7	46 ± 3.1	48 ± 3.1	51 ± 3.4	<0.001
$(a\text{-}v)O_2$ (mL O_2/dL)	P	2.8 ± 0.3	1.9 ± 0.2	2 ± 0.1	2 ± 0.1	<0.001
	M	3.5 ± 0.1	2.1 ± 0.2	2.1 ± 0.2	2.2 ± 0.2	<0.001
OER	P	0.18 ± 0.02	0.12 ± 0.01	0.12 ± 0.01	0.12 ± 0.01	<0.001
	M	0.19 ± 0.02	0.12 ± 0.02	0.13 ± 0.03	0.14 ± 0.03	<0.001
$Paco_2$ (kPa)	P	4.75 ± 0.11	4.5 ± 0.12	4.68 ± 0.11	4.48 ± 0.10	
	M	4.68 ± 0.09	4.6 ± 0.11	4.58 ± 0.12	4.47 ± 0.12	

All values are expressed as mean ± SEM.

Vo_2I, indexed oxygen consumption; $(a\text{-}v)O_2$, arteriovenous difference in oxygen contents; OER; oxygen extraction ratio; P, 2 mg/kg intravenous propofol followed by 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol infusion; M, 2 mg/kg intravenous methohexital followed by 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ methohexital infusion.

[a]Within-group one-factor analysis of variance with repeated measures.

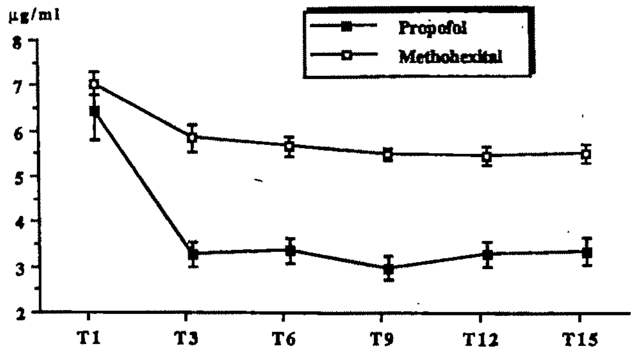

Figure 4. Whole blood propofol concentrations after intravenous administration of 2 mg/kg of propofol followed by 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol infusion; and plasma methohexital concentrations after intravenous administration of 2 mg/kg of methohexital followed by 100-$\mu g \cdot kg^{-1} \cdot min^{-1}$ methohexital infusion (mean ± SEM).

sial (6,22). The decrease in stroke index observed in our patients may reflect a predominant vascular effect on the venous side because the expected increase in cardiac index after arteriolar dilation did not occur.

It is interesting that our isotopic study showed evidence of altered left ventricular performance during methohexital anesthesia: global ejection fraction decreased as end-systolic volume increased, whereas end-diastolic volume did not change. Todd et al. (9) reported a similar depression of myocardial function during high-dose methohexital anesthesia, but contrary to our data, large volumes of fluid were needed to maintain stable filling pressures. In contrast, the cardiovascular effects of propofol can be attributed mainly to a decrease of preload: global ejection fraction and end-systolic volume remained stable.

Ejection fraction, considered as a good index of global left ventricular performance, is a complex function of contractility, preload, and afterload. Ejection fraction is preload- and afterload-dependent. Thus it is predictable that ejection fraction would not detect subtle changes in the myocardial contractile state. During propofol anesthesia, the fact that cardiac index and stroke index did not increase and end-systolic volume did not decrease when mean arterial pressure decreased may suggest a negative inotropic effect, being overbalanced by the vasodilation induced by propofol. A negative inotropic effect for propofol has been demonstrated in animal studies (6,23). Our previous report (7), as well as several human studies using load-dependent indicators of myocardial function, offered indirect evidence of the negative inotropic effect of propofol (8,24,25).

Assessment of contractility is difficult in the clinical setting in humans: ethical considerations do not allow the use of the instantaneous ventricular pressure-volume relationship introduced by Suga and coworkers (26). Nevertheless, the simple ratio of left ventricular peak systolic pressure to left ventricular end-systolic volume has been shown to be a sensitive indicator of left ventricular disease (27). In contrast to global ejection fraction, this relationship remains relatively independent of the loading conditions, more adequately reflecting intrinsic alterations in left ventricular performance. Recently, peak systolic arterial blood pressure or systolic cuff pressure and end-systolic volumes measured by radionuclide imaging have been substituted for ventricular end-systolic pressure and absolute end-systolic volumes, respectively (28,29). Thus we found it reasonable to report these data that suggest that the changes in left ventricular global ejection fraction were paralleled by the changes in the peak systolic arterial blood pressure–end-systolic volume ratio. If this semiinvasively obtainable pressure-volume ratio is also an index of contractility in the intact human left ventricle, our study showed that methohexital but not propofol has negative inotropic properties. Contrary to our findings, Mulier et al. (5) demonstrated negative inotropic properties for both propofol and thiopental, using peak arterial blood pressure and end-systolic volume measured with transesophageal echocardiography, in patients anesthetized with etomidate, vecuronium, and 70% nitrous oxide in oxygen.

In summary, the present study highlights differences in the etiology of the cardiovascular depression induced by propofol and methohexital administered to patients with coronary artery disease and good left ventricular function, and maintained preoperatively with nitrates and calcium-channel blockers. Propofol decreases preload and globally preserves left ventricular performance as assessed with global ejection fraction; a negative inotropic effect masked by vasodilation is discussed. Methohexital reduces left ventricular global ejection fraction and increases end-systolic volume without preload change, indicating negative inotropic properties.

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Hemodynamic Responses to Endotracheal Extubation After Coronary Artery Bypass Grafting

Robert Paulissian, MD, M. Ramez Salem, MD, Ninos J. Joseph, BS, Berton Braverman, PhD, Howard C. Cohen, MD, George J. Crystal, PhD, and Harold J. Heyman, MD

Department of Anesthesiology, Illinois Masonic Medical Center, Chicago, Illinois

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After coronary artery bypass grafting (CABG) surgery, patients may remain at risk for myocardial ischemia and infarction and ventricular dysrhythmias. The hemodynamic responses to endotracheal extubation and the efficacy of intravenous lidocaine pretreatment were studied after CABG surgery and overnight mechanical ventilation. Twenty-five patients were divided into two groups: group 1 ($n = 13$) patients who had tracheal extubation after pretreatment with a placebo; group 2 patients who received lidocaine (1 mg/kg IV) before tracheal extubation. Hemodynamic data, electrocardiographic tracings, and arterial blood gases were obtained before tracheal extubation, during suctioning, and 1, 5, and 20 min after tracheal extubation. Group 1 patients displayed significant increases in heart rate, arterial blood pressure, rate-pressure product, right atrial pressure, and cardiac index during suctioning and within 1 min of tracheal extubation, returning to preextubation level by 5 min. There were no significant changes in pulmonary and systemic resistance indices. Hemodynamic changes in group 2 patients were similar to those in group 1. Both in the absence and presence of lidocaine, tracheal extubation caused hemodynamic responses that were small in magnitude and brief in duration. These responses were not associated with electrocardiographic or enzymatic evidence of myocardial ischemia or infarction, or with ventricular dysrhythmias. Compared with the well-documented hemodynamic responses to tracheal intubation, we found that extubation of the trachea after CABG surgery was associated with less pronounced responses. This may be related to avoidance of laryngoscopy and possibly accommodation to the endotracheal tube. These modest hemodynamic responses of extubation of the trachea after CABG surgery were not modified by intravenous lidocaine.

(Anesth Analg 1991;73:10–5)

After coronary artery bypass grafting (CABG) surgery, patients may remain at risk for myocardial ischemia and infarction (1) and ventricular dysrhythmias (2). This has been attributed to several factors. First, some vessels with >70% occlusion are not surgically bypassed (3) and, in the absence of adequate collateral blood flow, the areas of the myocardium perfused by these vessels might remain vulnerable to ischemia. Second, distal coronary disease may prevent adequate runoff in those vessels surgically bypassed (3). Third, zones surrounding areas of prior myocardial infarction may trigger ventricular dysrhythmias, particularly during stress-induced catecholamine release (4). Thus, measures to prevent imbalances between myocardial supply and demand after CABG surgery may be important.

Although the hemodynamic responses to endotracheal intubation have been extensively studied (5–8), the hemodynamic consequences of extubation have received little attention. Coughing during suctioning and endotracheal extubation may cause tachycardia, hypertension, and excessive catecholamine release, thus increasing myocardial oxygen demands. Bidwai and associates (9,10) investigated the heart rate (HR) and arterial blood pressure (MAP) response to extubation in essentially healthy patients undergoing elective general, orthopedic, and gynecologic operations. They found significant increases in HR and MAP that persisted for 6–8 min and that these responses were attenuated by the intravenous administration of lidocaine before extubation (9). Comparable increases in HR, MAP, or other hemodynamic alterations might be detrimental in patients after CABG surgery. The present study was undertaken to examine the hemodynamic and electrocardiographic (ECG) responses associated with endotracheal extubation after CABG surgery. In light of the findings of Bidwai et al. that prior treatment with intravenous

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Accepted for publication April 21, 1991.

Address correspondence to Dr. Paulissian, Department of Anesthesiology, Illinois Masonic Medical Center, 836 West Wellington Avenue, Chicago, IL 60657.

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0003-2999/91/$3.50

lidocaine blunted the increase in HR and MAP, the efficacy of prior treatment with intravenous lidocaine was also evaluated.

Methods

The experimental protocol was approved by the institutional review board, and informed consent was obtained from 40 patients scheduled to undergo elective CABG surgery. Patients with valvular heart disease, cardiac dysrhythmias, and pacemakers were excluded from the study. Demographic data, preoperative cardiac medications, indices of cardiac function (left ventricular end-diastolic pressure and ejection fraction), and number of diseased vessels (>70% occlusion) reported during preoperative cineangiocardiography were obtained from the patients' charts. All cardiac medications were continued throughout the intraoperative period.

On arrival to the operating suite, intravenous, radial artery, and triple-lumen thermodilution pulmonary artery catheters were percutaneously inserted under local anesthesia. Anesthesia was induced intravenously with 50–75 μg/kg of fentanyl and 0.1 mg/kg of pancuronium followed by endotracheal intubation with an appropriately sized, cuffed orotracheal tube. Anesthesia was maintained with additional doses of fentanyl (total dose = 100–150 μg/kg IV) and pancuronium. The operation then progressed in a routine fashion. After the completion of the operation, the patients were transferred to the Surgical Intensive Care Unit and were mechanically ventilated overnight using a Bennett MA I respirator in a synchronized intermittent mandatory ventilatory (SIMV) mode. The tidal volume, SIMV rate, and inspired oxygen fraction ($\mathrm{FIO_2}$) were set to maintain the arterial carbon dioxide tension ($\mathrm{Paco_2}$) between 35 and 43 mm Hg and the arterial oxygen tension ($\mathrm{Pao_2}$) ≥90 mm Hg. Sedatives and narcotics were administered as needed to facilitate ventilatory support during the early hours after operation but were discontinued approximately 6 h before anticipated endotracheal extubation. The $\mathrm{FIO_2}$ was gradually reduced from 0.6 to 0.4, the $\mathrm{FIO_2}$ at which tracheal extubation was attempted.

On the morning of the first postoperative day, the hemodynamic status and ventilatory variables were evaluated. Patients who required circulatory support (intravenous inotropes or vasodilators or intraaortic balloon counterpulsation) on the morning of the first postoperative day were excluded from the study. If the circulatory status of the patient appeared stable, arterial blood gas values, portable chest radiographs, and respiratory variables were used to evaluate the feasibility of weaning from respiratory support. The criteria to begin weaning from mechanical ventilation included a fully awake patient, no abnormal findings on chest radiograph, $\mathrm{Paco_2}$ between 35 and 45 mm Hg, $\mathrm{Pao_2} \geq 90$ mm Hg ($\mathrm{FIO_2} = 0.4$), a negative inspiratory force ≥ 25 cm H_2O, and a vital capacity ≥10 mL/kg. When the patient met the above criteria for weaning, the mandatory breaths during SIMV were progressively decreased from 8 to 4 breaths/min, and serial analysis of arterial blood gases was performed. Endotracheal extubation was considered feasible if the patient was hemodynamically stable, $\mathrm{Paco_2}$ remained between 35 and 45 mm Hg, $\mathrm{Pao_2} \geq$ 90 mm Hg ($\mathrm{FIO_2} = 0.4$), negative inspiratory force ≥ 25 cm H_2O, and vital capacity ≥ 15 mL/kg at an SIMV rate of 4 breaths/min.

After the criteria for tracheal extubation were met, the patients were randomly assigned to one of two groups. In group 1 (n = 13), a placebo injection of 0.9% sodium chloride was administered 2 min before endotracheal extubation. The respirator was disconnected then and was replaced by assisted ventilation with a self-inflating bag (15-L O_2 flow) for several large breaths before the endotracheal tube and oropharynx were suctioned. The self-inflating bag was then reconnected for several more large breaths while the endotracheal tube cuff was deflated and the endotracheal tube was withdrawn. After tracheal extubation, O_2 with heated aerosol was administered by mask at 5-L flow for the remainder of the study period. In group 2 (n = 12), the patients received an intravenous bolus injection of 2% lidocaine (1 mg/kg) 2 min before suctioning followed by extubation in the manner described above. The persons performing the extubation and recording hemodynamic and respiratory data were not informed as to whether a placebo or lidocaine was administered.

The following variables were measured or derived from appropriate formulas: HR, MAP, cardiac index (CI), rate-pressure product (RPP), right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), stroke volume index (SVI), systemic vascular resistance index (SVRI), and pulmonary vascular resistance index (PVRI). Electrocardiographic tracings, leads II and V_5, were obtained at each measurement period. All measurements were recorded at (a) 5 min before extubation, (b) during suctioning of the airway, (c) immediately after extubation, (d) 5 min after extubation, and (e) 20 min after extubation. In addition, arterial and mixed venous blood gas samples were drawn before tracheal extubation and 5 and 20 min after extubation.

The ECG tracings obtained at each measurement interval were evaluated by a cardiologist who was not informed as to whether the patient received lidocaine. Electrocardiographic evidence of new myocardial ischemia was defined as ST-segment changes

Table 1. Demographic Data

	Group 1	Group 2
n	13	12
Age (yr)	60.6 ± 3.1	57.7 ± 2.8
Sex		
Male	10	7
Female	3	5
BSA (m^2)	1.91 ± 0.04	1.90 ± 0.06
LVEDP (mm Hg)	11.1 ± 1.2	9.9 ± 1.5
Ejection fraction	53.9 ± 4.1	55.6 ± 4.7
No. of diseased vessels	3.2 ± 0.2	3.1 ± 0.2
Preoperative β-blockade	12	11

BSA, body surface area; LVEDP, left ventricular end-diastolic pressure. All values except *n*, sex, and preoperative β-blockade are mean ± SEM.

of ≥1.0 mm measured 80 ms beyond the J point (11–13). Perioperative myocardial infarction (MI) was suspected when any of the following was present: acute ST-segment elevation with or without T-wave abnormalities unresponsive to nitrates or calcium channel blockers; appearance of new Q-waves >0.04 s, or ST-segment depression with deeply inverted T-waves in the absence of Q-waves (14). Confirmation of suspected MI was obtained if creatinine phosphokinase (CPK) was >500 U/L and the isoenzyme CPK-MB was >3% (15). These CPK measurements were done within the first 3 h immediately postoperatively and daily during the intensive care stay.

Significant differences between and within groups were identified by a multivariate analysis of variance for repeated measures and the Student-Newman-Keuls test. Demographic differences between groups were analyzed with the Student's *t*-test for continuous variables and the Mann-Whitney U-test for discrete data. Statistical significance was accepted when $P < 0.05$.

Results

Of the original 40 patients who consented to the study, 25 patients met all the criteria for tracheal extubation and inclusion in the study on the morning of the first postoperative day. These patients were randomly assigned to group 1 (placebo, 13 patients) or group 2 (lidocaine, 12 patients). Demographic data including age, sex, body surface area (BSA), preoperative cardiac medications, preoperative cardiac status, and number of grafts were not different between the two groups and are shown in Table 1. Hemodynamic and blood gas data appear in Tables 2 and 3. Group 1 patients had slightly higher preextubation values for RAP, MPAP, and PCWP and lower SVRI as compared with those in group 2 patients (Table 2).

In group 1, HR was increased modestly during suctioning and immediately after tracheal extubation. Heart rate returned to the preextubation level by 5 min after extubation and remained essentially unchanged at 20 min. Mean arterial blood pressure, RPP, and CI increased in parallel with HR during suctioning and immediately after tracheal extubation, returning to control level by 5 min after tracheal extubation. There were no changes in PCWP, SVI, SVRI, PVRI, pHa, Paco$_2$, or Pao$_2$ (Tables 2 and 3).

In the lidocaine-treated patients (group 2), HR also increased during suctioning and immediately after extubation. By 5 min after tracheal extubation, the HR had returned to the preextubation level. Mean arterial blood pressure was significantly increased during extubation. Mean pulmonary artery pressure, PCWP, and RAP were increased during suctioning and extubation, respectively. Rate-pressure product, CI, SVI, SVRI, PVRI, pHa, Paco$_2$, and Pao$_2$ did not change during the study in group 2 (Tables 2 and 3).

No patients in either group required reintubation or showed ECG or enzymatic evidence of myocardial ischemia or infarction intraoperatively or postoperatively. All patients had uneventful recovery and were discharged from the hospital.

Discussion

The reported incidence of postoperative MI after CABG surgery varies between 2.8% and 31% (16). The wide disparity seems to depend on the sensitivity of the diagnostic techniques used to detect MI (16). Force and associates (1), studying risk stratification of postoperative MI after CABG surgery, found that low postoperative ejection fraction (<40%) and inadequate revascularization were major contributing factors to the incidence of postoperative MI. Others have suggested additional factors including the presence of prebypass myocardial ischemia (17), severity of coronary artery disease (18), longer bypass or aortic cross-clamp times (17,19), age over 65 yr (19), and unstable angina (20).

In the present study, the hemodynamic responses to tracheal extubation (Table 2) were both short-lived (<5 min in duration) and moderate. At maximum (extubation measurement period), HR was only increased by 12% and MAP by 20%. The absence of cardiac dysrhythmias or ECG and CPK isoenzyme evidence of myocardial ischemia or infarction indicates the lack of clinical consequences of these changes. Our results are in agreement with Elia et al. (21) who found that tracheal extubation was associated with minimal hemodynamic responses in a limited number of CABG patients.

Other facts may have contributed to the lack of more pronounced hemodynamic effects. The selec-

Table 2. Hemodynamic Data

	Before extubation	Suctioning	During extubation	After extubation	
				5 min	20 min
HR (beats/min)					
Group 1	90.8 ± 3.7	99.2 ± 6.3^a	101.4 ± 6.9^a	90.3 ± 3.5	88.5 ± 3.6
Group 2	85.1 ± 8.6	95.9 ± 8.6^a	94.0 ± 5.5^a	85.1 ± 4.9	85.0 ± 4.7
MAP (mm Hg)					
Group 1	87.8 ± 4.4	101.6 ± 4.1^a	105.4 ± 7.2^a	92.4 ± 4.6	89.6 ± 4.7
Group 2	93.5 ± 4.1	98.7 ± 5.6	104.2 ± 4.8^a	95.0 ± 4.5	94.4 ± 4.8
RPP					
Group 1	8,080.5 ± 639.8	10,509.8 ± 885.6^a	11,024.7 ± 894.9^a	8,462.1 ± 671.9	8,064.5 ± 691.7
Group 2	8,054.9 ± 762.3	9,611.4 ± 965.9	9,845.4 ± 810.5	8,032.1 ± 571.6	8,072.8 ± 749.6
CI ($L \cdot min^{-1} \cdot m^{-2}$)					
Group 1	3.9 ± 0.2	4.6 ± 0.3^a	4.9 ± 0.4^a	3.9 ± 0.2	3.6 ± 0.2
Group 2	3.8 ± 0.2	3.9 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	3.7 ± 0.2
SVI (mL/m^2)					
Group 1	48.2 ± 3.2	48.7 ± 4.3	53.1 ± 3.8	46.5 ± 1.4	44.4 ± 2.1
Group 2	44.1 ± 2.6	39.2 ± 2.4^b	42.5 ± 2.9^b	45.7 ± 3.7	43.9 ± 2.6
SVRI ($dyne \cdot cm^{-2} \cdot s^{-1} \cdot m^{-2}$)					
Group 1	1,396.1 ± 71.5	1,803.2 ± 374.4	1,666.8 ± 303.5	1,706.0 ± 281.5	1,807.1 ± 321.1
Group 2	1,996.6 ± 252.2^b	2,051.2 ± 152.0	2,115.9 ± 266.0	2,090.4 ± 363.0	2,018.8 ± 237.8
RAP (mm Hg)					
Group 1	12.9 ± 1.6	14.4 ± 1.0^a	14.2 ± 1.1^a	12.0 ± 1.6	11.8 ± 1.5
Group 2	9.0 ± 1.1^b	10.4 ± 1.2^b	10.3 ± 1.2^{a,b}	10.1 ± 1.8	8.9 ± 1.4
MPAP (mm Hg)					
Group 1	22.5 ± 1.7	25.8 ± 2.6	26.8 ± 2.5^a	23.1 ± 1.3	23.2 ± 1.1
Group 2	15.6 ± 0.9^b	19.2 ± 1.0^{a,b}	19.6 ± 1.1^{a,b}	17.4 ± 0.8^b	16.3 ± 0.7^b
PCWP (mm Hg)					
Group 1	12.7 ± 1.6	13.9 ± 1.5	14.1 ± 1.5	13.4 ± 1.8	13.3 ± 1.9
Group 2	9.9 ± 0.9^b	11.5 ± 1.2^a	10.9 ± 1.3	11.3 ± 1.3	11.1 ± 1.1
PVRI ($dyne \cdot cm^{-2} \cdot s^{-1} \cdot m^{-2}$)					
Group 1	149.0 ± 15.7	192.1 ± 44.5	194.2 ± 46.9	202.2 ± 42.1	211.6 ± 45.1
Group 2	152.9 ± 11.7	152.0 ± 23.2	189.6 ± 26.9	133.5 ± 22.1^b	158.5 ± 38.4

HR, heart rate; MAP, mean arterial blood pressure; RPP, rate-pressure product; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; RAP, right atrial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index.

Values are mean ± SE.

[a] Significantly different from the preextubation value ($P < 0.05$).

[b] Significantly different from the control value ($P < 0.05$).

Table 3. Blood Gas Data

	Before extubation	After extubation	
		5 min	20 min
pHa			
Group 1	7.423 ± 0.010	7.435 ± 0.010	7.412 ± 0.006
Group 2	7.414 ± 0.014	7.405 ± 0.018	7.410 ± 0.015
$Paco_2$ (mm Hg)			
Group 1	37.9 ± 1.5	37.3 ± 1.9	39.3 ± 1.3
Group 2	28.2 ± 1.3	39.6 ± 2.1	38.8 ± 1.4
Pao_2 (mm Hg)			
Group 1	112.4 ± 10.0	126.2 ± 11.9	106.2 ± 8.3
Group 2	116.9 ± 9.5	114.6 ± 8.7	107.2 ± 6.7

pHa, arterial pH; $Paco_2$, arterial carbon dioxide tension; Pao_2, arterial oxygen tension.

Values are mean ± SE.

tion criteria excluded patients with valvular heart disease, cardiac dysrhythmias, and pacemakers, and those patients requiring circulatory or inotropic support after operation, and necessarily eliminated some patients with poorer myocardial function or with more unstable hemodynamics. It is possible that the hemodynamic and ECG responses to extubation may be more pronounced in these patients. Furthermore, residual effects of β-adrenergic blocking drugs may have obtunded the hemodynamic responses to tracheal extubation. Most of our patients (23 of 25 patients) were receiving preoperative β-adrenergic blocking drugs (60–160 mg/day), which were continued through the intraoperative period. Although β-adrenergic blocking drugs were withheld in the postoperative period before tracheal extubation, residual β-blockade may have somewhat attenuated the ability of the heart to respond to reflex stimuli. The benefit of preoperative β-adrenergic blockade has been previously demonstrated (22,23).

In contrast to the present study, Bidwai et al. (9) reported that pretreatment with intravenous lidocaine (1 mg/kg) was effective in blunting the HR and blood pressure responses to suctioning and extubation in essentially healthy patients who had undergone noncardiac surgery. The difference in findings between the two studies may be related to the different patient groups studied. Another possibility may be the different anesthetic states in the two groups. In the study by Bidwai et al. (9), halothane and 50% nitrous oxide were used and tracheal extubation occurred immediately after completion of the surgical procedure in the operating room. At the time of suctioning and extubation, their patients were still under a light plane of anesthesia. It is possible that the light plane of anesthesia and the general anesthetic effect of intravenous lidocaine may have combined to blunt the cardiovascular responses.

Larger doses (1.5–2.0 mg/kg) of intravenous lidocaine have been advocated to suppress the cough reflex and cardiovascular stimulation associated with endotracheal intubation and to prevent laryngospasm after extubation (8,24–26). Although the use of larger doses to attenuate the hemodynamic responses to extubation have not been studied, it must be stressed that intravenous lidocaine can cause transient respiratory depression in some patients (27).

In a previous study, with a similar patient population undergoing CABG surgery, we found that endotracheal intubation was accompanied by hemodynamic responses sufficient to produce myocardial ischemia (28). Thus it appears that extubation is less stressful than intubation, perhaps because laryngoscopy is avoided and some degree of accommodation to the endotracheal tube occurs (21). The modest hemodynamic responses to tracheal extubation after CABG surgery were not modified by intravenous lidocaine, and it therefore appears that routine pretreatment with intravenous lidocaine would be of little value for tracheal extubation. However, this does not preclude the use of lidocaine in those patients at risk of developing cardiac dysrhythmias.

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Isoflurane Impairs the Function of Ischemic Myocardium in Acutely but Not in Chronically Instrumented Dogs

Nikolaus Mayer, MD, Michael Zimpfer, MD, and Karl Steinbereithner, MD

Department of Anesthesia and General Intensive Care, University of Vienna; Ludwig Boltzmann Institute for Experimental Anesthesiology and Research in Intensive Care, Vienna, Austria

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To compare the effects of isoflurane on ischemic myocardium in acutely and chronically instrumented animals, 12 mongrel dogs were monitored with electromagnetic or Doppler ultrasonic flow transducers and hydraulic occluders around the left circumflex coronary artery, pressure transducers in the left ventricle, and heparin-filled catheters in the descending aorta. Regional function of normal and ischemic myocardium was assessed by sonomicrometry. The hemodynamic effects of isoflurane (2% inspired concentration) were more pronounced in the acutely than in the chronically instrumented dogs. Decreases in mean arterial pressure (−47% ± 5% in the acute and −22% ± 4% in the chronic preparation, $P < 0.01$), left ventricular contractility (−51% ± 6% and −33% ± 4%, $P < 0.01$), and coronary perfusion pressure (−59% ± 6% and −12% ± 9%, $P < 0.01$) were more distinct in the acutely instrumented animals. Although the reduction of regional function during isoflurane anesthesia was similar in normal myocardium in both preparations (−33% ± 4% acute and −34% ± 6% chronic preparation, not a significant difference), an exaggerated dysfunction was observed in the ischemic myocardium of the acutely instrumented dogs (−66% ± 2% and −30% ± 4%, $P < 0.01$). It is concluded that acutely instrumented dogs respond to the hemodynamic effects of isoflurane, resulting in ischemic myocardial dysfunction, significantly more than do chronically instrumented dogs.

(Anesth Analg 1991;73:16–24)

Isoflurane causes vasodilation in the systemic and coronary circulation (1). Although lowering preload and afterload might have beneficial effects in patients with coronary artery disease, the coronary vasodilator properties of isoflurane are, perhaps, associated with the ability to induce a redistribution of coronary blood flow away from ischemic myocardium by increasing flow to normal myocardium, i.e., "coronary steal."

Since Reiz et al. (2) reported electrocardiographic and metabolic signs of myocardial ischemia in patients with coronary artery disease during isoflurane anesthesia, the effect of this volatile anesthetic on coronary hemodynamics and its possible ability to induce coronary steal have been a matter of continuing anesthesiologic interest and investigation. In particular, major concern centers on whether isoflurane could be the cause of intraoperative myocardial ischemia, even though heart rate and arterial pressure, determinants of myocardial oxygen consumption clinically, have been controlled carefully.

Investigational approaches to this problem have been performed mainly in animals. Canine studies yielded conflicting results. Buffington et al. and Priebe and Foëx, for example, reported that isoflurane evokes regional myocardial dysfunction in acute, closed- (3), and open-chest (4) preparations, whereas Cason et al. (5), in an experimental setup similar to that used by Buffington and Priebe, found no incidence of coronary steal during either isoflurane or halothane anesthesia. Moreover, Warltier and associates (6) even reported improvement in the function of postischemic myocardium during isoflurane and halothane anesthesia in chronically instrumented dogs.

The basis of the present study was the validity of the assumption that the conflicting results regarding the potential of isoflurane to cause coronary steal with a consequent further impairment of the function of ischemic myocardium are due primarily to the use of acute, open-chest preparations as opposed to use

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Supported in part by grants from the Österreichische Nationalbank, the Medizinisch-Wissenschaftlicher Fonds des Bürgermeisters der Bundeshauptstadt Wien, and the Hochschuljubiläumsstiftung der Stadt Wien, and a research grant from the Bundesministers für Wissenschaft und Forschung.

Accepted for publication February 22, 1991.

Address correspondence to Dr. Mayer, Department of Anesthesia and General Intensive Care, University of Vienna, Spitalgasse 23, A-1090 Vienna, Austria.

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0003-2999/91/$3.50

of chronic, intact-animal techniques. Therefore, we compared the effects of 2% isoflurane on coronary hemodynamics and on the function of myocardium rendered ischemic to comparable degrees by single-vessel coronary occlusions on the left circumflex coronary arteries in chronically and acutely, nearly identically instrumented dogs.

Methods

Approval from the Institutional Committee on Animal Research and from the Ethics Committee of the Faculty of Medicine, University of Vienna, was obtained for this study.

Chronic Instrumentation

Seven mongrel dogs of either sex, weighing between 16 and 24 kg, were chronically instrumented so that hemodynamic measurements could be made during subsequent experiments. Anesthesia was induced with thiopental (15 mg/kg IV) and maintained with enflurane (2.0%–2.5%, inspired concentration). A thoracotomy was performed through the fifth left intercostal space, the pericardium was incised, and the heart was exposed. A miniature pressure gauge (Konigsberg Instruments Inc., Pasadena, Calif.) was inserted into the left ventricle through a stab wound in the apex, and heparin-filled catheters (Tygon, Acron, Ohio) were implanted in the descending aorta and in the left atrium. The left circumflex coronary artery (LCX) was dissected free a few millimeters below the edge of the left atrial appendage, and a Doppler ultrasonic flow transducer and a hydraulic cuff occluder were placed around the vessel. A ligature was tied around the freed LCX, distal to the flow transducer, with a 20-gauge needle along its side. The needle was then immediately removed, and the LCX was stenosed to a degree that approximately equaled the diameter of a 20-gauge needle. Two pairs of ultrasonic crystals were implanted in subendocardial layers of normal and ischemic areas parallel to the short axis of the heart (Figure 1). Although the ultrasonic crystals of the normal segment are within an area supplied by the left anterior coronary artery, the ischemic segment is located in the LCX-supplied region. Before the insertion of the crystals into the ischemic segment, the LCX was occluded at the site of the Doppler flow probe until myocardial cyanosis was observed. The crystals were then implanted in the center of the cyanotic region. All catheters and cables were run subcutaneously and exteriorized in the interscapular area. Although strict aseptic procedures were observed at all times, the dogs were given cefamandole (50 mg/kg IM) for 3 days postoperatively.

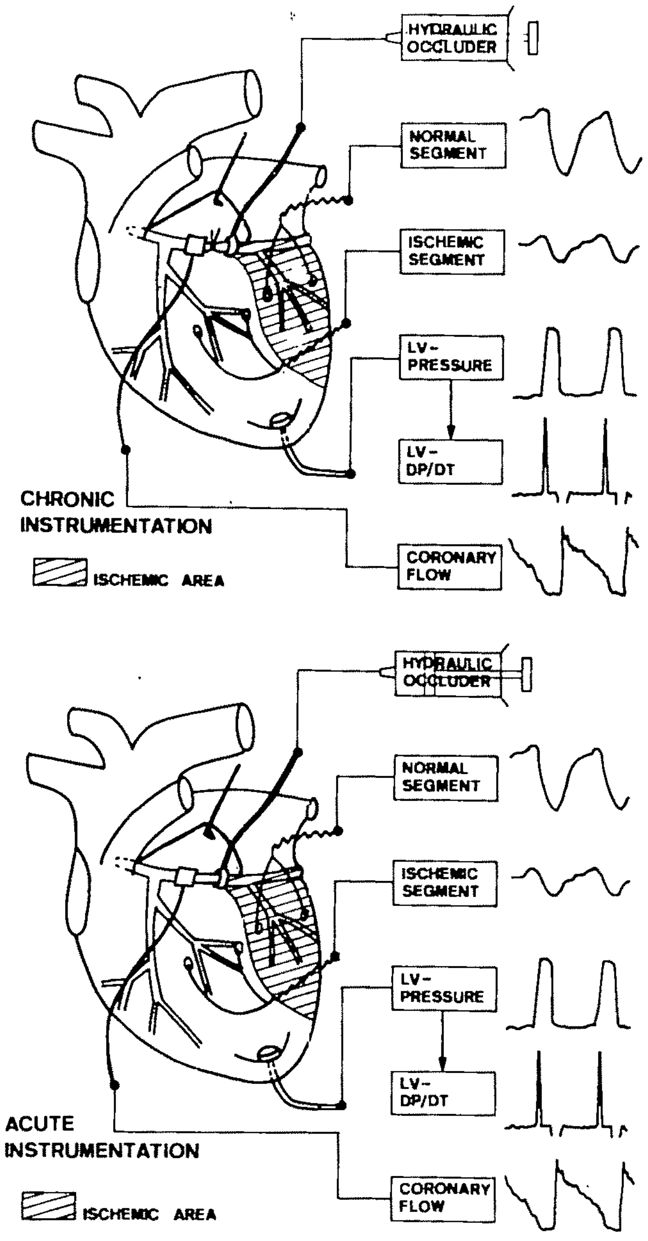

Figure 1. Instrumentation technique. The similarity between the chronic instrumentation (*above*) and the acute instrumentation (*below*) is evident and an essential requirement for comparing these two experimental approaches. A miniature pressure gauge was implanted in the left ventricle and a hydraulic occluder and a flow probe were placed on the LCX. Although in the chronic preparation the vessel was permanently narrowed by a ligature, coronary stenosis in the acute preparation was conducted with the hydraulic occluder alone. Pairs of ultrasonic crystals were implanted in normal and ischemic areas. The schematic tracings at the right show segment shortening in normal and ischemic segments, left ventricular pressure, dP/dt, and coronary flow.

Experiments were performed 2–5 wk after surgery. None of the dogs had arrhythmias or systemic infections, and all could exercise normally. While the conscious unsedated dogs reclined quietly, continuous measurements of arterial pressure, left ventricular pressure, the time rate of change of pressure (dP/dt), myocardial segment lengths, and heart rate were made. Absence of reactive hyperemia after a 20-beat coronary occlusion was either confirmed or the hydraulic cuff occluder on the LCX was gradually further inflated until absence of reactive hyperemia pointed toward exhaustion of the subendocardial coronary vasodilator reserve, which was indicative of the presence of critical coronary stenosis. According to Gallagher (7) and Gross (8) and their associates, critical coronary stenosis can be defined as the minimal degree of stenosis that is necessary to eliminate a reactive hyperemic response after release of the stenosis without changing mean coronary blood flow. It required two to four repetitive occlusions to establish the critical coronary stenosis in the present study. Anesthesia was then induced with propofol (6 mg/kg IV) (n = 2) or by administering isoflurane with a canine anesthesia mask (n = 5). The trachea was intubated, and constant-volume intermittent positive-pressure ventilation at a rate of 14 breaths/min with a mixture of oxygen and air (F_{IO_2} = 0.3) was instituted to produce normocapnia and to keep the arterial oxygen tension around 100 mm Hg. Isoflurane (2%, inspired concentration) was supplied by a vaporizer calibrated by a gas chromatograph in our laboratory. After 45 min of isoflurane anesthesia, steady-state hemodynamic parameters were recorded assuming a near complete equilibration with the anesthetic gas.

Acute Instrumentation

Five mongrel dogs of either sex, weighing between 17 and 28 kg, were acutely instrumented for hemodynamic measurements during subsequent experiments. Basically, the dogs were instrumented in almost exactly the same way as the chronically instrumented animals (Figure 1). Anesthesia was induced with thiopental (15 mg/kg IV) and the analgesic piritramide (2.0–3.5 mg/kg IV). The trachea was intubated, and intermittent positive-pressure ventilation was accomplished with a rate of 14 breaths/min. The adequacy of gas exchange and acid-base balance (Corning 168 pH/Blood Gas Analyzer, Corning Medical, Medfield, Mass.) as well as normal electrolyte parameters (Radiometer Kopenhagen, Sodium-Potassium-Analyzer, Copenhagen, Denmark) was checked repeatedly throughout the entire experiment. Anesthesia was maintained with a continuous infusion of piritramide (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$) and N_2O in O_2 (F_{IO_2} = 0.3). The instrumentation was carried out as described above for the chronically instrumented dogs except that the flow in the LCX was measured with an electromagnetic flowmeter system (Gould, model SP 2202, Gould Inc., Cleveland, Ohio) and critical stenosis was instituted with the hydraulic cuff occluder alone. The dogs were given 4–6 $mL \cdot kg^{-1} \cdot h^{-1}$ of normal saline during the surgical preparation and the subsequent experiment.

After completion of the surgical preparation, the critical coronary stenosis on the LCX was accomplished with the hydraulic cuff occluder and a three-way stopcock. When the reactive hyperemic response after a 20-beat coronary occlusion was blunted, the newly established coronary hemodynamic situation and the overall cardiovascular status after the acute instrumentation were allowed to stabilize for at least 30 min. The piritramide infusion was then discontinued, and air was substituted for N_2O. Isoflurane (2 vol%, inspired concentration) was supplied by the calibrated vaporizer. To assure nearly complete equilibration of the anesthetic gas, at least 45 min elapsed before the responses to isoflurane were recorded. If adjustments of the acid-base status, the respiratory pattern, or the volume status were necessary, they were made no later than 30 min before the start of the experiment.

The positions of the ultrasonic crystals of both the chronic and the acute experimental preparation were confirmed at autopsy. Minimal fibrosis extending <1 mm from the crystal was observed at the site of implantation in the chronically instrumented dogs. If the crystals were not in the endocardial third of the left ventricular wall, the data were discarded (n = 2, chronic preparation).

Experimental Measurements

The miniature pressure gauges were calibrated in vitro before implantation and in vivo by matching the left ventricular pressure tracing with the left atrial pressure and the systolic aortic pressure. Regional myocardial function was determined by sonomicrometry, i.e., continuous registration of the segment length between the pairs of the ultrasonic crystals, based on the measurement of the travel time of the ultrasonic impulse. The accuracy of the measurement, determined by the frequency of the crystals (5 MHz), is about 0.2 μs, which corresponds to a distance of 0.3 mm. For evaluation of regional myocardial function, the segment tracings were recorded at a paper speed of 50 mm/s. End-diastolic segment length (EDSL) was defined as the beginning of the sharp upslope of the left ventricular pressure tracing (dP/dt) and end-systolic segment length (ESSL) by the dicrotic notch in the aortic pressure signal.

The following formulas were used for calculation of derivatives of the length signal:

$$SL = EDSL - ESSL,$$

where SL is segment length;

$$SL\% = (SL \times 100)/EDSL,$$

where SL% is percent segment length; and

$$SW = SL \times MAP,$$

where SW is segment work and MAP is mean arterial blood pressure.

Left circumflex coronary blood flow was determined by an ultrasonic Doppler flowmeter in the chronically instrumented dogs and with an electromagnetic flowmeter in the acutely instrumented animals. Both systems have been described and compared in detail previously (9). In the chronically instrumented dogs electrical zero blood flow was determined repeatedly and was finally confirmed by calibration. In all experiments an adequate signal-to-noise ratio was determined by displaying the flow signal on an oscilloscope and listening to the audio Doppler signal. In the case of inaccuracies owing to poor acoustical coupling between transducer and blood vessel or an inadequate signal-to-noise ratio, the recorded data were not utilized ($n = 1$). The following formulas were used for calculation of coronary flow, conductance, and perfusion pressure:

$$CBF = FD \times A^2,$$

where CBF is coronary blood flow, FD is Doppler frequency shift, and A^2 is the cross-sectional area of the coronary vessel;

$$CC = CBF/MAP,$$

where CC is coronary conductance and MAP is mean arterial pressure; and

$$CPP = DAP - LVEDP,$$

where CPP is coronary perfusion pressure, DAP is diastolic arterial blood pressure, and LVEDP is left ventricular end-diastolic pressure.

The relationship between velocity, as determined by the Doppler flowmeter, and volume flow is linear as long as the cross-sectional area of the blood vessel within the transducer remains constant. This linear relationship between velocity and volume flow has been demonstrated repeatedly and confirmed by timed collections of blood flow. At the time of autopsy, the vessel was firmly attached to the flow transducer by a fibrous scar, making changes of the cross-sectional area of the vessel within the flow transducer unlikely. In the acutely instrumented dogs, occlusive zero flow was determined at the end of the experiments by inflating the hydraulic cuff occluder on the circumflex coronary artery. The electromagnetic flow probes were calibrated with timed collections of blood when the animals were killed. Coronary conductance was calculated with the above-cited formula.

Data Analysis

The data were recorded on a multichannel magnetic tape recorder (Honeywell, model 101, Denver, Colo.) and played back on a direct writing oscillograph (Gould Recorder, model 2800, Cleveland, Ohio). A cardiotachometer, triggered by the signals of the pressure pulse, provided instantaneous and continuous records of heart rate. Results are expressed as mean ± SEM. Significant differences of baseline values and responses to 2% isoflurane between the conscious/chronic and the anesthetized/acute preparation were determined using the group *t*-test. The effects of isoflurane were compared with the control period using the *t*-test for paired data. A *P* value of less than 0.05 was accepted as statistically significant.

Results

Chronic Instrumentation

Effects of isoflurane on systemic hemodynamics. Because anesthesia induction had no significant effect, the data from the two different induction sequences were pooled. Critical constriction of the LCX had no impact on global left ventricular function in the conscious animals (Figure 2, Table 1). Isoflurane caused an increase in heart rate (48% ± 11%, mean ± SEM) and progressive decreases of left ventricular systolic pressure (27% ± 5%), the maximum rate of left ventricular pressure rise (dP/dt) (33% ± 4%), mean arterial pressure (22% ± 4%) (Figure 3), and segment work in both normal (48% ± 5%) and ischemic (51% ± 3%) segments (Table 1).

Effects of isoflurane on coronary hemodynamics and regional myocardial function. Isoflurane caused no significant changes in flow and in perfusion pressure in the critically constricted LCX. However, as a result of the decrease of mean arterial pressure, coronary conductance increased 67% ± 23% ($P < 0.05$, Table 2). As a consequence of the critical constriction of the LCX, the ischemic segments were contracting 42% less than the segments supplied by the left anterior coronary artery ($P < 0.01$, Figures 2 and 4). Isoflurane caused a considerable depression of the function of the ischemic (30% ± 4%, $P < 0.01$) and the normal (34% ± 6%, $P < 0.05$) segments but neither an exaggerated nor a permanent myocardial dysfunction of the ischemic segments was detected (Figures 2 and 3).

Acute Instrumentation

Effects of acute instrumentation on systemic and coronary hemodynamics and regional myocardial function. In comparison with the conscious state in the chroni-

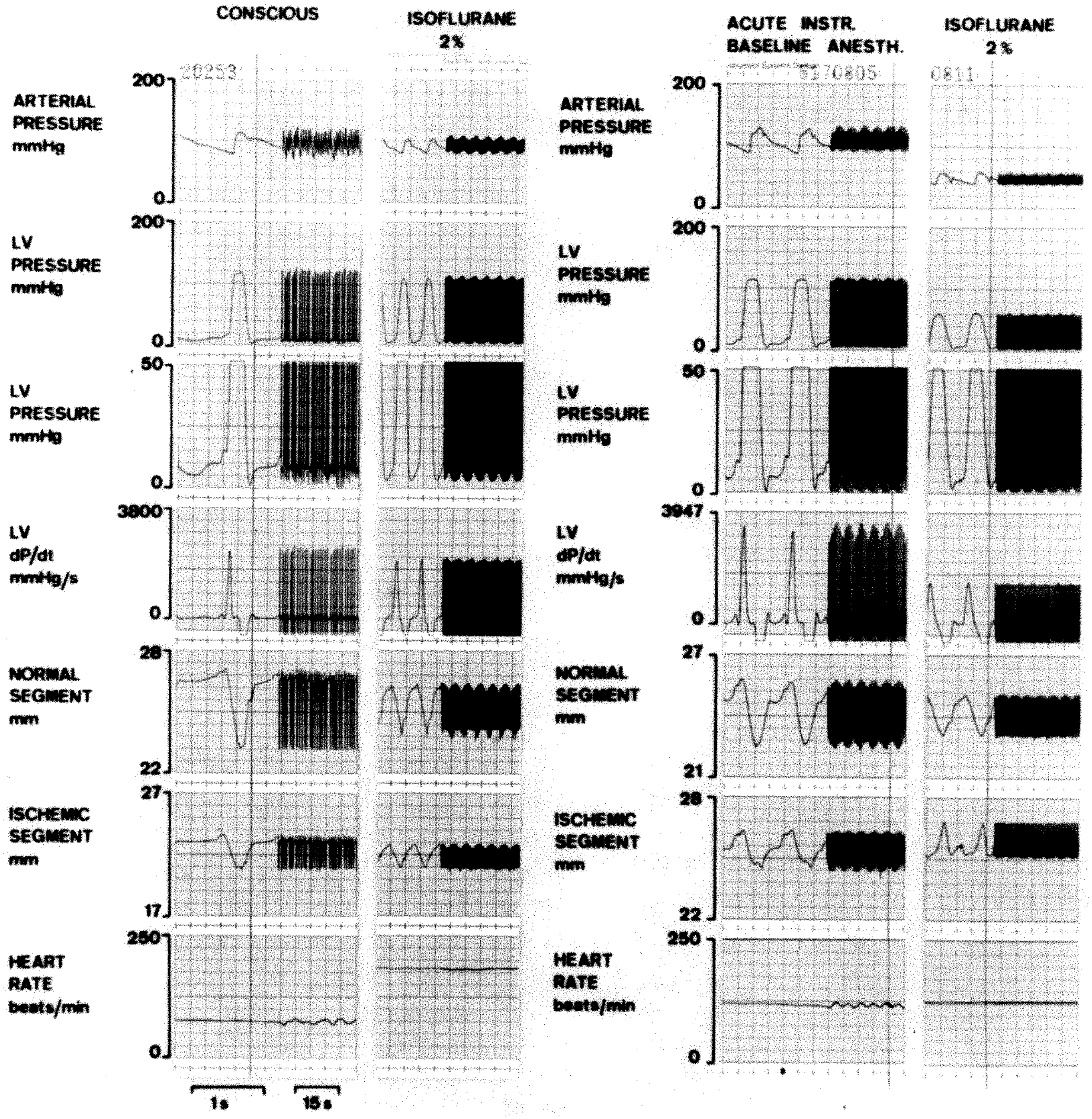

Figure 2. Typical global and regional hemodynamic responses to isoflurane. In the chronically instrumented dog (left-hand panel) during conscious control, shortening in the ischemic segment was less than in the normal segment and no global left ventricular dysfunction was detected. Isoflurane decreased the contractile function of both segments without causing exaggerated ischemic myocardial dysfunction. In the acutely instrumented dog (right-hand panel) isoflurane caused an exaggerated dysfunction of the ischemic segment indicated by pronounced dyskinesia and hypokinesia. In addition, arterial pressure, left ventricular pressure, and LV-dP/dt were reduced remarkably.

cally instrumented dogs, acute instrumentation with baseline anesthesia was accompanied by increases in mean arterial pressure and decreases in the left ventricular end-diastolic pressure and in normal and ischemic segment work (Figure 2, Table 1). By contrast, no effect of acute instrumentation and baseline anesthesia on left circumflex coronary flow, conductance, and perfusion pressure was observed (Table 2).

As a consequence of the critical constriction of the LCX, the ischemic segments were contracting 54% less than the segments supplied by the left anterior coronary artery (Figures 2 and 4). Although, in the open-chest anesthetized preparations, contraction of normal and ischemic segments was less than in the conscious dogs, the relationship between normal and ischemic myocardium was not different in the two series of experiments (Figure 4).

Table 1. Global and Regional Hemodynamic Parameters in Chronically and Acutely Instrumented Dogs

	Chronic instrumentation		Acute instrumentation	
	Conscious	2% Isoflurane	Baseline anesthesia	2% Isoflurane
HR (beats/min)	88 ± 3	130 ± 7[a]	100 ± 8	103 ± 10[b]
MAP (mm Hg)	92 ± 3	71 ± 3[a]	102 ± 7[b]	54 ± 7[a,c]
LVSP (mm Hg)	121 ± 3	89 ± 6[a]	117 ± 7	66 ± 8[a,b]
LVEDP (mm Hg)	13 ± 1	9 ± 2[d]	8 ± 1[c]	6 ± 1
LV-dP/dt (mm Hg/s)	2596 ± 119	1737 ± 96[a]	2196 ± 118	1078 ± 149[a,c]
NSSW (mm·mm Hg)	418 ± 59	205 ± 41[d]	246 ± 88[b]	91 ± 55[a,c]
ISSW (mm·mm Hg)	287 ± 22	142 ± 40[a]	131 ± 38[c]	23 ± 10[a,c]

Values are expressed as mean ± SEM.

HR, heart rate; MAP, mean arterial pressure; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; SP, systolic pressure; NS, normal segment; IS, ischemic segment; SW, segment work.

[a] $P < 0.01$, 2% isoflurane significantly different from the conscious state or from baseline anesthesia.

[b] $P < 0.05$, acute instrumentation significantly different from chronic instrumentation.

[c] $P < 0.01$, acute instrumentation significantly different from chronic instrumentation.

[d] $P < 0.05$, 2% isoflurane significantly different from the conscious state or from baseline anesthesia.

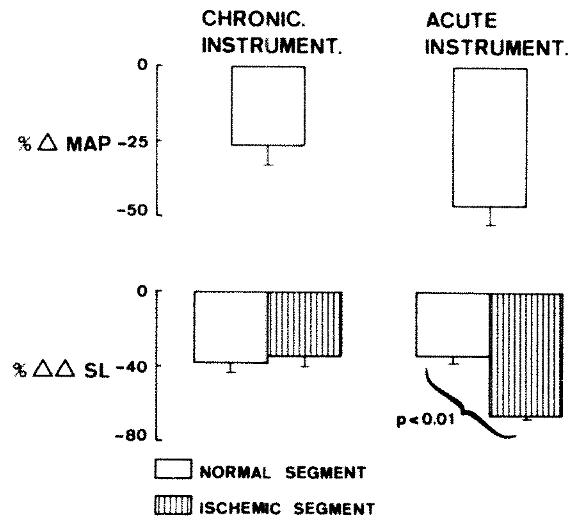

Figure 3. Relative changes of mean arterial pressure and segment shortening with isoflurane. In the intact, chronic preparation the decrease of mean arterial pressure was moderate and the reduction of shortening in normal and ischemic myocardium was uniform. By contrast, the acute, open-chest preparation was characterized by a dramatic decrease in arterial pressure together with an exaggerated dysfunction of ischemic myocardium.

Effects of isoflurane on systemic hemodynamics. Isoflurane caused drastic reductions of left ventricular systolic pressure (44% ± 5%), the maximum rate of left ventricular pressure rise (dP/dt) (51% ± 6%), and mean arterial pressure (47% ± 5%) ($P < 0.01$, Figures 2 and 3). Normal and ischemic segment work decreased by 64% ± 5% and 82% ± 2%, respectively ($P < 0.01$, Table 1).

Effects of isoflurane on coronary hemodynamics and regional myocardial function. Left circumflex coronary flow did not change significantly with isoflurane. Whereas coronary perfusion pressure decreased by 59% ± 6% ($P < 0.01$), coronary conductance was augmented by 73% ± 20% ($P < 0.05$, Table 2). Again, isoflurane caused a distinct reduction of the function of the ischemic (66% ± 2%, $P < 0.01$) and the normal (33% ± 4%, $P < 0.01$) segments; in contrast to the intact dogs, however, an exaggerated dysfunction of the ischemic segments was detectable (Figures 2 and 3).

Discussion

The principal finding of this study is that canine hemodynamic responses to isoflurane are profoundly influenced by the mode of instrumentation to which the animals are subjected. The most pronounced differences were changes observed in arterial blood pressure and regional myocardial function. In the chronically instrumented dogs, the decrease in function of normal and ischemic myocardium during isoflurane anesthesia was uniform. By contrast, in the acutely instrumented animals an exaggerated ischemic myocardial dysfunction presented as either hypokinesia or akinesia ($n = 3$), or even as paradoxical bulging during systole ($n = 2$). This type of wall-motion abnormality, identified previously as a reliable index of myocardial ischemia (10), is most likely the result of a substantial decrease in myocardial oxygen supply owing to a reduction of coronary perfusion pressure after isoflurane administration in the acutely instrumented animals. By looking at the reciprocal values for coronary resistance, i.e., coronary conductance, the decrease of coronary perfusion pressure may even be underestimated because—perhaps due to simultaneous changes in wall tension—coronary blood flow was not decreased to the same extent.

The function of ischemic myocardium might be

Table 2. Coronary Hemodynamics in Chronically and Acutely Instrumented Dogs After Establishing Critical Coronary Constriction

	Chronic instrumentation		Acute instrumentation	
	Conscious	2% Isoflurane	Baseline anesthesia	2% Isoflurane
LCXCBF (mL/min)	39 ± 5	48 ± 7	39 ± 2	35 ± 3
LCXCC (mL·min^{-1}·mm Hg^{-1})	0.41 ± 0.05	0.66 ± 0.09[a]	0.40 ± 0.05	0.71 ± 0.14[a]
CPP (mm Hg)	69 ± 3	60 ± 5	78 ± 8	32 ± 6[b,c]

Values are expressed as mean ± SEM.

LCX, left circumflex coronary artery; CBF, coronary blood flow; CC, coronary conductance; CPP, coronary perfusion pressure.

[a] $P < 0.05$, 2% isoflurane significantly different from the conscious state or from baseline anesthesia.

[b] $P < 0.01$, 2% isoflurane significantly different from the conscious state or from baseline anesthesia.

[c] $P < 0.01$, acute instrumentation significantly different from chronic instrumentation.

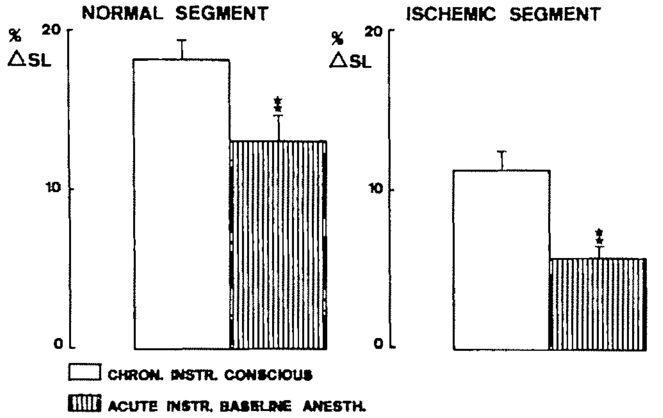

Figure 4. Comparisons of segment shortening during the control period. Although, due to the effects of baseline anesthesia, both segments in the acutely instrumented dogs were contracting less than in the chronically instrumented animals, the degree of ischemic dysfunction, as indicated by the reduced shortening of the ischemic segment relative to the normal segment, was of comparable magnitude in the two series of experiments.

imperiled by increases in heart rate, wall tension, and contractility, each of which increases myocardial oxygen demand (11). By analyzing the heart rate responses to isoflurane in both preparations in parallel with the conduct of ischemic myocardium, it is noteworthy that in the chronically instrumented animals, in spite of an increase of heart rate, no exaggerated dysfunction of ischemic myocardium was detected. Conversely, in the acutely instrumented animals there was ischemic myocardial deterioration even though heart rate remained unchanged after isoflurane administration. This suggests that in dogs subjected to the present experimental conditions, ischemic myocardial function is dependent more on adequate coronary perfusion pressure provided by physiological heart rates than on normal diastolic filling periods.

By looking at the remaining determinants of myocardial oxygen demand, wall tension, i.e., preload (LVEDP) and afterload (MAP), and contractility (LV-dP/dt), it is interesting to note that acute instrumentation was associated with significantly lower preload levels during the control period and showed a tendency to decrease further with isoflurane. Although not different during the control period, isoflurane reduced contractility more in the acute than in the chronic preparation. Because of the beneficial effects of low preload and contractility on myocardial function, it is tempting to speculate that the deterioration of ischemic myocardium in the acutely instrumented animals would have been even more pronounced if both parameters had been of comparable magnitude in the two experimental preparations. Parenthetically, in quantification of the dissimilar negative inotropic effects of isoflurane in the two series of experiments, it has to be stated that the preload dependency of LV-dP/dt is a typical characteristic of acute but not of chronically instrumented animals (12). Thus, the pronounced reduction of LV-dP/dt in the acutely instrumented dogs not only is a result of isoflurane's negative inotropic effect but also reflects the low preload level of anesthetized, open-chest preparations.

The distinctly more sensitive responses of the acutely instrumented dogs to isoflurane are a result of a combination of factors. Basal anesthesia, for example, not only has a depressant effect on cardiac function but also affects the peripheral vasculature and interferes with integrative cardiocirculatory control (13–15). Mechanical ventilation impedes venous return and reduces cardiac filling pressures, i.e., preload. Therefore, although in fact stroke volume and systolic pressure decrease, concomitant surgery with sympathetic stimulation of the peripheral vasculature and the heart and consequent increases in arterial pressure and tachycardia may mask hypotensive and/or hypovolemic states, which might then be unmasked by isoflurane. Finally, recent surgical trauma and rapid development of hypothermia (16), with their profound impact on circulatory homeostasis, as well as spontaneous deterioration of the acute preparation (17) also have to be taken into account.

There is the possibility, however remote, that the different responses of ischemic myocardium in the chronic and the acute preparation are due, at least in part, to the development of collateral vessels in the intact dogs. There is some reason to believe that formation of collaterals, if at all, is of only minor importance in our chronically instrumented animals. These reasons involve, among others, the stable hypokinesia of ischemic myocardium over 5 wk, which otherwise would have regained normal contraction patterns by this time (18). In addition, canine collaterals tend to develop in subepicardial layers (19), whereas our ultrasonic crystals were inserted in the subendocardium, where occurrence of ischemia is most likely. The fact remains that, although the extent of myocardial dysfunction in terms of segment shortening was comparable in the ischemic areas of both acutely and chronically instrumented dogs, the different responses are, at least in part, due to the different duration of ischemia.

Because of different experimental protocols as well as type, severity, and number of coronary obstructions, contributions to the controversy regarding the effects of isoflurane on ischemic myocardium are hard to compare. However, as far as the acute preparation is concerned, our findings confirm those of Priebe and Foëx (4), who also observed ischemic myocardial dysfunction associated with isoflurane-induced hypotension in an acute, open-chest preparation. It is interesting to note that in their study critical coronary stenosis was not accompanied by ischemic dysfunction of myocardium supplied by the stenosed vessel as in our experiments. This might be due to the different methods used to establish critical stenosis, i.e., vasodilation by physiologic means through inflation and deflation of the hydraulic cuff occluder with consequent adenosine release versus systemic injection of a coronary vasodilator acetate. Therefore, it is obvious that the degree of stenosis termed critical was not the same in the two studies; preexisting ischemic myocardial dysfunction points toward a more severe coronary stenosis in our experiments.

In an acute, open-chest preparation, Tatekawa et al. (20) detected no regional ischemic dysfunction in myocardium supplied by a critically constricted circumflex coronary artery when isoflurane was added to baseline anesthesia consisting of a continuous pentobarbital infusion. Remarkably, this finding is paralleled by a myocardial blood flow pattern indicative of transmural coronary steal and is thus at variance with the concept of a close relationship between myocardial flow and function (21). These discrepancies from our own acute preparation can be interpreted on the basis of different mean arterial pressure levels (80 mm Hg in Tatekawa's study, 54 mm Hg in our experiments) that were achieved with different isoflurane concentrations (1.2 vs 1.6 MAC for the dog) and by different levels of preexisting ischemia. During the establishment of critical stenosis, the duration of the occlusion of the circumflex coronary artery was shorter in Tatekawa's study (5 s vs 20 beats), imposing a smaller hypoxic challenge on myocardium and probably a lower degree of coronary stenosis. Hence, wall thickening, before isoflurane administration, was only 18% less in the area supplied by the stenosed vessel than in the control area. In our dogs the ischemic segments were contracting 54% less than the normal segments. Finally, the pentobarbital infusion also has to be taken into account with respect to the effects of barbiturates on vascular smooth muscle tone (22).

In summary, acutely and chronically instrumented dogs demonstrated quite different hemodynamic responses to 2% isoflurane, the most dramatic being the behavior of ischemic myocardium. Although in the chronic preparation isoflurane reduced the function of normal and ischemic myocardium to a similar degree, an exaggerated dysfunction of ischemic myocardium was detected in comparison with normal myocardium in the acute preparation. Although the deterioration of ischemic myocardium in these dogs is rather the consequence of their more sensitive responses to the hemodynamic effects of isoflurane than of coronary steal, regional blood flow redistribution phenomena cannot be excluded entirely on the basis of the present data. The results of this study not only stress the profound impact of baseline anesthesia and recent surgery on hemodynamic variables, they also emphasize the need to distinguish precisely between findings obtained from chronic and those obtained from acute experimental approaches as the outcome might well be different.

The authors thank H. Gilly, PhD, G. Dworacek, E. Sailer, and R. Schwarz for their expert technical work, and E. Kotai for her graphic work.

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Effects of Atracurium and Pancuronium on the Oculocardiac Reflex in Children

J. Loewinger, MD, I. Friedmann-Neiger, MD, M. Cohen, MB, ChB, and E. Levi, MD

Department of Anesthesia and Intensive Care, Beilinson Medical Center, Petah-Tiqva and Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

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The authors compare the effect of two muscle relaxants, atracurium and pancuronium, on the bradycardia resulting from the oculocardiac reflex during eye surgery for strabismus in children. Two groups, each composed of 15 children, received either pancuronium or atracurium during strabismus operations. Heart rate and rhythm were observed at several points during the operations, and the changes that occurred in the two groups were compared. We found that the incidence and severity of the bradycardia, the incidence of dysrhythmias, and the need for atropine administration were significantly greater in the atracurium group than in the pancuronium group.

(Anesth Analg 1991;73:25–8)

The oculocardiac reflex (OCR), first described by Aschner (1) and Dagnini (2) in two simultaneous but independent reports at the beginning of this century, occurs during eye surgery for strabismus. Several reports indicate that the OCR occurs not only during operation on the eye muscles but also during procedures involving other facial structures (3,4). This reflex is also called the trigeminal-vagal reflex and usually produces bradycardia, and occasionally, chaotic dysrhythmias or sinoatrial arrest.

Although nondepolarizing muscle relaxants have been recommended as an adjunct for anesthetic management during strabismus operations, they differ in their respective cardiovascular effects. Pancuronium increases heart rate owing to its vagolytic action and to its action on the sympathetic nervous system (5,6), whereas atracurium and vecuronium do not produce significant changes in the heart rate (6,7). Although the influence of tubocurarine, alcuronium, pancuronium, and vecuronium on the OCR has been studied, the influence of atracurium has not been determined (8). Because atracurium is commonly used, we examined and compared it with pancuronium with regard to the OCR.

Methods

Thirty healthy children (ASA physical status I), aged between 1.5 and 10 yr and undergoing strabismus operation, were studied after obtaining the approval of the institutional ethics committee and the informed consent of the children's parents. The children were randomly divided into two groups according to the muscle relaxant received: the pancuronium group and the atracurium group. All the children received droperidol intramuscularly, 200 μg/kg to a total dose of 5 mg, 30–45 min before the induction of anesthesia. No atropine was given. On the child's arrival in the operating room, surface electrodes were attached to provide electrocardiographic monitoring of lead 1 (Datascope 871 ECG monitor). Arterial blood pressure was measured noninvasively every 5 min by use of an Accutorr 2A automatic blood pressure monitor. An inhaled induction of anesthesia was performed with halothane, N_2O, and O_2. After venous cannulation, 2 μg/kg of fentanyl was injected, and the halothane concentration was lowered to 0.25%–0.5%. Either 100 μg/kg of pancuronium or 500 μg/kg of atracurium was then given. The lungs were ventilated for 3 min with N_2O/O_2 (60%/40%), and orotracheal intubation was performed. Anesthesia was maintained with N_2O/O_2 (60%/40%) and with 0.25%–0.5% halothane. The minute volume was adjusted to maintain an end-tidal partial pressure of carbon dioxide in the range of 30–35 mm Hg. During surgery supplementary doses of the muscle relaxant, one-fifth of the original tracheal intubating dose, were

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Accepted for publication April 4, 1991.

Address correspondence to Dr. Loewinger, Department of Anesthesia and Intensive Care, Beilinson Medical Center, Petah Tiqva 49100, Israel.

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0003-2999/91/$3.50

Table 1. General Data About the Children

Drug group	Sex M	Sex F	Age (yr)	Weight (kg)	No. of muscles operated on
Pancuronium	6	9	5 ± 3	18 ± 6	35
Atracurium	7	8	6 ± 2	21 ± 6	39

Values are mean ± SD.

Table 2. Mean Heart Rate[a] During Several Stages of Anesthesia

Drug group	Awake	Before muscle relaxant	After intubation
Pancuronium	101 ± 19[b]	105 ± 23[b]	121 ± 22[c]
Atracurium	96 ± 17[b]	95 ± 17[b]	92 ± 24[c]

[a] In beats per minute.
[b] No significant difference between groups ($P > 0.1$).
[c] Significant difference between groups ($P < 0.01$).

added when clinically indicated (a return of muscle tone in the fingers or a reduction of the respiratory compliance). Supplementary 1-μg/kg doses of fentanyl were given when the heart rate increased more than 20 beats/min and/or when the systolic arterial blood pressure increased more than 20 mm Hg in response to surgical stimulation.

The heart rate was recorded before induction of anesthesia, before and after giving the muscle relaxant, before and after tracheal intubation, and before and during traction on the extraocular muscles; the minimum heart rate during the operation was also noted. If the operation included more than two muscle corrections, only those changes noted during the first and second muscle corrections were recorded. The difference in the heart rate before and during muscle traction was calculated. If the heart rate decreased below 50 beats/min or if dysrhythmias occurred, the surgeon was requested to cease traction on the eye muscle, and 20 μg/kg of atropine was injected.

At the end of surgery, 40 μg/kg of neostigmine and 20 μg/kg of atropine were administered to antagonize any residual neuromuscular blockade. The oculocardiac reflex was considered to occur when the reduction in the heart rate exceeded 20% of the rate before muscle traction. The results in the two groups were compared and were analyzed for statistical significance by the two-sample t-test.

Results

The data concerning the children and the operation are shown in Table 1 (all results are rounded to the nearest integer). The age, weight, and sex distribution, and the number of muscles operated on were similar for the two groups. In the pancuronium group, one supplementary dose of muscle relaxant was given to four children, and two supplementary doses were given to two children. In the atracurium group, one supplementary dose was given to five children, two supplementary doses were given to two children, and three supplementary doses were given to one child.

Several children, three in the pancuronium group and four in the atracurium group, had heart rate decreases of more than 20% when the conjunctiva was pulled and cut. In neither group was there a need to add atropine.

The heart rate at several stages of the anesthesia is shown in Table 2. Atracurium had no effect on the heart rate, whereas pancuronium accelerated the heart rate moderately. Table 3 shows the heart rate before and during muscle traction. In the atracurium group, the heart rate before traction was lower than in the pancuronium group and was also significantly lower than the awake values. In contrast, in the pancuronium group, the heart rate values before muscle traction were higher than the awake values.

In both groups, there was a significant decrease in the heart rate during muscle traction. During the first muscle traction, the decrease in heart rate was significantly greater in the atracurium group than in the pancuronium group. The difference in the incidence of OCR between the pancuronium and atracurium groups observed during the first muscle traction apparently disappeared during the second muscle traction. The groups undergoing three or more mus-

Table 3. Mean Heart Rate[a] Before and During Muscle Traction

Drug group	First traction *n*	First traction Before	First traction During	Second traction[b] *n*	Second traction[b] Before	Second traction[b] During
Pancuronium	15	120 ± 17	94 ± 25[c]	12	113 ± 18	85 ± 30[c]
Atracurium	15	86 ± 20	34 ± 22[c]	5	79 ± 11	51 ± 13[c]

[a] In beats per minute.
[b] Noted only for those children who did not receive atropine after the first muscle traction.
[c] Significant decrease in heart rate ($P < 0.001$) during the two muscle tractions in both groups.

Table 4. Minimum Heart Rate During Operation and the Incidence of Oculocardiac Reflex and Dysrhythmias in the Two Muscle Relaxant Groups

Drug group	Minimum heart rate during operation (beats/min)	First traction			Second traction[a]		
		n	Bradycardia[b]	Dysrhythmias	*n*	Bradycardia[b]	Dysrhythmias
Pancuronium	76 ± 22	15	9 (60%)	0 (0%)	11	6 (55%)	1 (9%)
Atracurium	33 ± 21	15	14 (93%)	6 (40%)	5	4 (80%)	1 (20%)

[a] Noted only for those children who did not receive atropine after the first muscle traction.
[b] Decrease of heart rate of more than 20%.

cle corrections were too small for any valid statistical analysis. Atropine was not given to any patient in the pancuronium group during the first muscle traction; one patient required atropine during the second muscle traction and one during the third muscle traction. In the atracurium group, however, nine patients required atropine during the first muscle traction and one patient during the second muscle traction. In fact, in four children in this group sinus arrest developed for periods exceeding 5 s but reverted to normal sinus rhythm on the cessation of muscle traction and the intravenous administration of atropine.

The incidence of the OCR (bradycardias and dysrhythmias) was significantly more frequent and the minimum heart rate throughout the operation was significantly lower in the atracurium group than in the pancuronium group (Table 4). We also noted that there was no significant difference between the two groups in the incidence of the OCR during the first or the second muscle traction in children who had not been given atropine before the second muscle traction.

Discussion

Karhunen et al. (8) examined the effects of tubocurarine, alcuronium, pancuronium, and vecuronium on the OCR (also defined as a decrease in heart rate of at least 20% or as the occurrence of dysrhythmias). Pancuronium had a mild protective effect against the OCR in comparison with tubocurarine and vecuronium, which were associated with significant decreases in heart rate during eye muscle traction. We cannot explain why pancuronium had only a mild protective effect against the OCR in the Karhunen et al. study, whereas it showed a strongly protective effect in our cases. However, in that previous study 10 μg/kg of atropine was administered intramuscularly 30–45 min before the induction of anesthesia. Atropine may mask the OCR by accelerating the heart rate, or may even produce bradycardia and arrhythmia by itself in the relatively small doses given intramuscularly in that study (9).

In our study, the incidence and magnitude of the OCR, as determined by the occurrence of arrhythmias or bradycardia, were more in the atracurium group (95%) than in the pancuronium group (60%). Atropine was also more frequently needed in the atracurium group. The explanation for this difference may be the vagolytic effect of pancuronium on the heart (5,6) as well as the direct and indirect sympathetic effects and the muscarinic blocking effect that pancuronium possesses.

We can only speculate why the difference in the incidence of OCR between the pancuronium and atracurium groups observed during the first muscle traction apparently disappeared during the second muscle traction. The five children remaining in the study in the atracurium group during the second muscle traction (after excluding all those children who had a severe bradycardia and received atropine during first muscle traction) may well comprise a population with a lower vagal tone, and therefore, are less susceptible to the vagal stimulation produced by muscle traction.

We conclude that clinicians who choose atracurium for such operations should consider prophylactic administration of atropine before traction on the extraocular muscles or should at least be vigilant regarding the high likelihood of bradycardia and dysrhythmias in response to stimulation. If for any reason the use of atropine is undesirable, pancuronium might be the preferred muscle relaxant.

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Scalp Infiltration With Bupivacaine in Pediatric Brain Surgery

Elizabeth J. Hartley, MD, PhD, Bruno Bissonnette, MD, Patrick St-Louis, PhD,
Juliette Rybczynski, PhD, and M. Elizabeth McLeod, MD

Departments of Anesthesia and Biochemistry, The Hospital for Sick Children, University of Toronto,
Toronto, Ontario, Canada

To evaluate whether local anesthetic scalp infiltration blunts hemodynamic responses to craniotomy in anesthetized children (age, 2–18 yr), two concentrations of bupivacaine (0.125% and 0.25%) with vasoconstrictor (epinephrine 1:400,000) were compared with control data when a solution of vasoconstrictor alone was injected. Arterial plasma levels of bupivacaine were measured by high-pressure liquid chromatography. Statistically significant increases in mean arterial pressure and heart rate above baseline measurements occurred in the control group during the period between scalp incision and dural reflection ($P < 0.05$). Both concentrations of bupivacaine prevented these increases. Mean arterial pressure and heart rate during scalp incision and scalp reflection were significantly higher in the control group than in both bupivacaine groups ($P < 0.05$). Peak bupivacaine plasma levels (mean ± SD) occurred either 5 or 10 min after infiltration and were significantly higher in the 0.25% group (0.48 ± 0.31 μg/mL) than the 0.125% group (0.14 ± 0.13 μg/mL) ($P < 0.05$). These results suggest that bupivacaine infiltration blocks the hemodynamic response to craniotomy. A concentration of 0.125% bupivacaine with 1:400,000 epinephrine is as effective as 0.25% bupivacaine with 1:400,000 epinephrine at reducing the hemodynamic response to craniotomy. Because the lower concentration of bupivacaine produces lower blood levels, we recommend 0.125% bupivacaine with 1:400,000 epinephrine as a useful, safe adjunct to general anesthesia in children undergoing craniotomy.

(Anesth Analg 1991;73:29–32)

When scalp and periosteal nerve endings are stimulated, blood pressure (BP) and heart rate (HR) increase (1). These effects may endanger the patient particularly in the presence of cerebrovascular anomalies, vascular tumors, or increased intracranial pressure (2). Intracranial hemorrhage caused by brain tumor is reported in children (3). By infiltrating the scalp with a local anesthetic to block nerve endings one would anticipate that this hemodynamic response could be prevented or diminished. In adults, bupivacaine (0.5% without epinephrine) has been shown to decrease significantly the expected hemodynamic response to scalp incision (1). This has not been previously demonstrated in children.

The purpose of this study was to compare the effect of two doses (0.125% and 0.25%) of bupivacaine with vasoconstrictor (epinephrine 1:400,000) and a control solution of vasoconstrictor alone on the hemodynamic responses to craniotomy in children.

Methods

Practical Procedures

With the approval from the hospital's Human Subjects Review Committee, written informed consent was obtained from the parents of 30 ASA physical status II or III children scheduled for elective supratentorial craniotomy. All children fasted, and none were premedicated preoperatively. Patients with a previous scalp incision or children under 2 yr of age were excluded from the study.

Anesthesia was induced with 5 mg/kg intravenous thiopental and 5 μg/kg fentanyl followed by 0.1 mg/kg pancuronium. Intravenous thiopental, 2 mg/kg, was administered immediately before tracheal intubation. After tracheal intubation, the lungs were ventilated with intermittent positive pressure at peak inspiratory pressures of 20–25 cm H_2O. Ventilation was adjusted to achieve an end-tidal P_{CO_2} of 26–30 mm Hg. Anesthesia

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Presented in part at the Forty-Seventh Annual Canadian Anaesthesia Meeting, June 1990, Vancouver, British Columbia, Canada.

Accepted for publication February 12, 1991.

Address correspondence to Dr. Hartley, Department of Anaesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada, M5G 1X8.

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0003-2999/91/$3.50

was maintained with 1% isoflurane (end-tidal concentration) in a mixture of oxygen-nitrous oxide (30%/70%). After induction a 22-gauge arterial line was inserted into the radial artery for BP monitoring and blood sampling.

Patients were assigned randomly, by means of code numbers, to one of three groups. The control group received a solution routinely used by neurosurgeons at the Hospital for Sick Children consisting of a saline solution with a vasoconstrictor (epinephrine 1:400,000). The investigational groups received bupivacaine (either 0.25% bupivacaine with 1:400,000 epinephrine or 0.125% bupivacaine with 1:400,000 epinephrine). The infiltration solution was prepared in a room separate from induction, and the anesthetist was unaware of the solution. Up to 1 mL/kg of assigned solution was injected subcutaneously by the surgeon along the proposed incision line. Five minutes elapsed before scalp incision.

The study period included measurements made at six times: (a) before scalp infiltration (baseline), for 3 min; (b) after scalp infiltration until just before scalp incision; (c) after scalp incision until just before reflection of the scalp flap; (d) during reflection of the scalp flap; (e) during opening of the cranial vault (when craniotome is in use); and (f) during dural incision. During each event, HR and mean arterial pressure (MAP) were recorded every 10 s. If BP rose 20% above control, additional isoflurane was administered.

Laboratory Procedures

To obtain blood samples for bupivacaine analysis, we first cleared the tubing dead space, removed an additional 10 mL of blood, then took the sample using a new syringe. Sampling times were preinfiltration and 5, 10, 15, 20, 30, 60, and 120 min after scalp infiltration. The blood was centrifuged and the plasma collected and stored at −20°C until analyzed by high-pressure liquid chromatography (4). Standards were prepared with dilutions of stock bupivacaine-HCl to give final concentrations of 0–500 μg/mL. Standards for extraction were prepared by adding 10 μL of each working standard to 990 μL of drug-free plasma to give concentrations of 0–5 μg/mL, respectively. The working solution of the internal standard contained 10 μg etidocaine/mL of distilled water. A standard curve of peak height ratio (bupivacaine/internal standard) versus concentration was constructed. The extraction procedure was as follows: 200 μL of standard or sample was mixed with 6 μL of internal standard solution. Sixty microliters of 1.0 M ammonium acetate (pH = 9.0) was added, and the mixture was vortexed for 20 s. Then 4 mL of ether was added, and the sample was vortexed, mixed on a rotator for 20 min, and then centrifuged at 1000 *g* for 10 min. Three milliliters of the ether phase was removed and added to 100 μL of 0.1 N HCl, vortexed, and centrifuged as before. The ether phase was discarded, and the acid phase was dried under nitrogen. The residue was reconstituted in 50 μL of distilled water. The high-pressure liquid chromatography was performed on a reversed-phase C8 (5-μm) column (Supelco; 4.6 15 cm) using acetonitrile/0.05 M ammonium phosphate, pH = 3.0: 45/55 as mobile phase. The flow rate was 1 mL/min and the eluate was monitored by ultraviolet detection at 210 nm.

Table 1. Demographic Data of Patients in the Three Groups

	Control	0.125% Bupivacaine	0.25% Bupivacaine
Male:female ratio	4:6	6:4	5:5
Age (yr)	11 ± 5	9 ± 3.5	8 ± 5.6
Weight (kg)	40 ± 22	33 ± 13.4	26 ± 13.4
Volume injected (mL/kg)	0.6 ± 0.3	0.5 ± 0.2	0.8 ± 0.3

All values, except for male:female ratio, are expressed as mean ± SD.

Statistical Analysis

The mean ± SD was determined for demographic data and peak serum bupivacaine levels and was compared using analysis of variance and the Student–Newman–Keuls test for multiple comparisons. Mean changes in BP and HR within each group during the study period were analyzed using repeated measures of analysis of variance and the Student–Newman–Keuls test for multiple comparisons. One-way analysis of variance and the Student–Newman–Keuls test were used to compare differences in the mean BP and HR between the three groups for each period of study. A linear regression analysis was used to determine the linearity between the highest and lowest values of the assay. A coefficient of variation was calculated from the lowest value by repeating the assay five times.

Results

All data are reported as mean ± SD. The three groups were well matched for age, sex, weight, and volume of infiltrate (Table 1). Recording periods for each event ranged from 40 to 250 s (112 ± 41 s). Hemodynamic changes in response to each event were compared with baseline (preinfiltration) recordings for each of the three groups. Neither MAP nor HR was

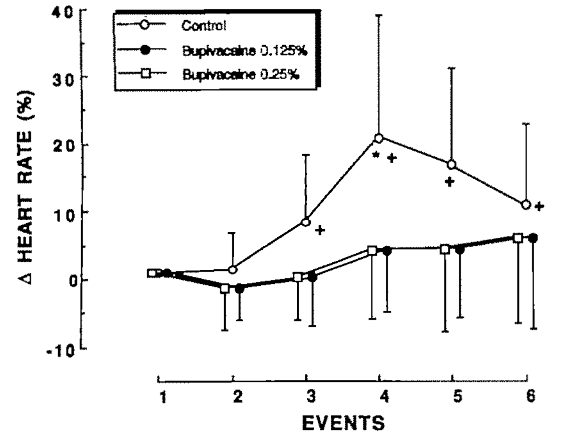

Figure 1. Mean percent changes in HR (beats/min) above levels before infiltration (baseline) up to opening of the dura. Bars indicate ± one standard deviation (SD). Events: (1) before scalp infiltration; (2) after scalp infiltration; (3) after scalp incision; (4) reflection of scalp flap; (5) craniotomy; (6) dural incision. *Statistically significant differences between control group (no bupivacaine) and bupivacaine groups ($P < 0.05$). +Statistically significant differences within a group compared with the baseline of that group ($P < 0.05$).

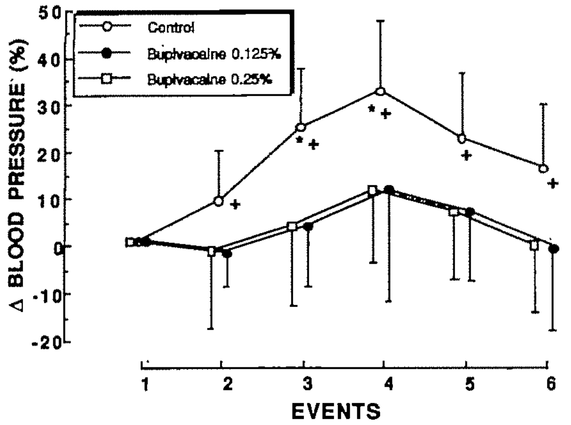

Figure 2. Mean percent changes in arterial BP (mm Hg) above levels before infiltration (baseline) up to the time of opening of the dura. Bars indicate ± one standard deviation (SD). Events: (1) before infiltration; (2) after scalp infiltration; (3) after scalp incision; (4) reflection of scalp flap; (5) craniotomy; (6) dural incision. *Statistically significant differences between control and bupivacaine groups ($P < 0.05$). +Statistically significant differences within a group compared with the baseline of that group ($P < 0.05$).

affected significantly by the process of infiltration in any of the three groups ($P < 0.05$) (Figures 1 and 2).

In the control group, scalp incision, scalp reflection, craniotomy, and dural incision all resulted in increases in MAP and HR significantly above baseline levels ($P < 0.05$). No significant hemodynamic responses occurred during any event in either of the groups receiving bupivacaine pretreatment ($P < 0.05$).

Table 2. Volume and Concentration of Bupivacaine Injected Into the Scalp and Peak Plasma Bupivacaine Levels in Each Patient in the 0.125% (1:400,000 epinephrine) and 0.25% (1:400,000 epinephrine) Bupivacaine Groups

Patient No.	Volume (mL/kg)	Concentration (mg/kg)	Peak plasma concentration (μg/mL)
Bupivacaine 0.125%			
1	0.81	1:02	0.10
2	0.03	1.04	0.22
3	0.48	0.61	0.06
4	0.48	0.57	ND
5	0.33	0.42	0.29
6	0.54	0.67	0.10
7	0.62	0.77	0.05
8	0.92	1.15	0.12
9	0.27	0.34	0.05
10	0.34	0.43	0.42
Mean ± SD	0.48 ± 0.26	0.70 ± 0.29	0.14 ± 0.13
Bupivacaine 0.25%			
11	1.42	3.57	0.57
12	0.90	2.25	0.63
13	0.92	2.30	0.96
14	0.50	1.25	0.29
15	0.86	2.16	0.11
16	0.41	1.03	0.25
17	0.48	1.21	0.21
18	0.91	2.27	0.35
19	0.80	2.00	0.24
20	0.57	1.44	0.27
Mean ± SD	0.78 ± 0.30	1.95 ± 0.75[a]	0.48 ± 0.31[a]

ND, not detectable.

[a] $P < 0.05$ compared with mean ± SD for 0.125% bupivacaine.

Hemodynamic responses to each event were then compared between each pair of the three groups (Figures 1 and 2). Baseline values in the study groups did not differ significantly from the control group. The average MAP and HR were significantly higher in the control group than in either bupivacaine-treated groups during scalp incision and reflection ($P < 0.05$). Control responses remained higher, but not significantly so, during craniotomy and dural incision ($P > 0.05$).

Peak arterial plasma levels of bupivacaine occurred at either 5 or 10 min after infiltration (Table 2). Mean ± SD peak levels after 0.25% bupivacaine were significantly higher (0.48 ± 0.31) than after 0.125% bupivacaine (0.14 ± 0.13) ($P < 0.05$). Larger volumes of infiltrate were used in the 0.25% bupivacaine group compared with the 0.125% group (Table 1). Although this difference was not significant ($P > 0.05$), it may have exaggerated the peak concentration differences. The highest level measured in this study was 1.06 μg/mL. This followed the injection of 2.2 mg/kg of 0.25% bupivacaine (with 1:400:000 epinephrine). No adverse reactions to infiltration were noted.

Retention times were 5.6 ± 0.4 and 4.9 ± 0.3 min for bupivacaine and etidocaine, respectively. Linearity was 0.025–5 μg/mL, limit of detection was 0.025 μg/mL, and the assay coefficient of variation was 5% at 1 μg/mL.

Discussion

In this study, increases in MAP and HR were attenuated by infiltrating the scalp with either 0.125% bupivacaine with 1:400,000 epinephrine or 0.25% bupivacaine with 1:400,000 epinephrine, compared with infiltrating with a vasoconstrictor solution alone, in children undergoing craniotomy. Moreover, we showed that the lower of the two concentrations of bupivacaine was as effective as the higher one and produced lower blood levels.

In a similar study of adult patients, Hillman et al. reported comparable hemodynamic attenuation using 0.5% bupivacaine without epinephrine (1). We added 1:400,000 epinephrine to our control and bupivacaine solutions and observed no increase in MAP and HR after infiltration, with the potential benefit of decreasing bupivacaine absorption and blood loss (5).

A concentration of 0.125% bupivacaine with 1:400,000 epinephrine was as effective as 0.25% bupivacaine with 1:400,000 epinephrine at controlling MAP and BP responses during scalp incision and reflection, when hemodynamic responses in the control group were greatest.

In our control group, although the MAP and HR began to decrease during the craniotomy and dural incision, they remained significantly above baseline levels. In the adult study, MAP and HR had returned to baseline by the time the dura was incised most probably because the dura is relatively insensitive to pain (1,6). The possible reasons that our control group had not returned to baseline are short skin incision to dural incision times and the persistent stimulation of scalp reflection.

Our data on time and concentrations of peak blood levels of bupivacaine are similar to those reported in a study of adults undergoing neuroleptanesthesia for seizure focus ablation (5). The toxic level of bupivacaine in infants and children has not been established, but has been extrapolated from data in adults and is thought to be 4 μg/mL (7). In infants and children, there is only one report of a blood level of bupivacaine after accidental intravenous injection; however, for obvious reasons the doses of bupivacaine to produce toxicity have not been systematically studied (8). No toxicity was reported after intercostal nerve blocks in children when 4 mg/kg of bupivacaine was used (9). The doses of bupivacaine used in this study should be well within the limits of safety.

In summary, responses of MAP and HR to scalp incision and reflection are attenuated by infiltrating the scalp with local anesthetic in children undergoing craniotomy. A 0.125% concentration of bupivacaine solution with 1:400,000 epinephrine is as effective as a 0.25% bupivacaine solution with 1:400,000 epinephrine in reducing hemodynamic responses. As the lower concentration of bupivacaine produces lower blood levels, we recommend the use of a 0.125% bupivacaine solution with 1:400,000 epinephrine to infiltrate the scalp 5 min before skin incision.

We thank Drs. H. Hoffman, R. Humphreys, B. E. Hendricks, and J. Drake and the Fellows and the Nurses of the Division of Neurosurgery for their cooperation and patience in the performance of this study.

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Vecuronium Infusion Requirements in Children During Halothane-Narcotic-Nitrous Oxide, Isoflurane-Narcotic-Nitrous Oxide, and Narcotic-Nitrous Oxide Anesthesia

Susan K. Woelfel, MD, Mai-Li Dong, MD, Barbara W. Brandom, MD, Joel B. Sarner, MD, and D. Ryan Cook, MD

Departments of Anesthesiology and Critical Care Medicine, Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

We were interested in determining the infusion rate of vecuronium required to maintain approximately 95% neuromuscular blockade in children during halothane-narcotic-nitrous oxide (0.8% end-tidal concentration), isoflurane-narcotic-nitrous oxide (1.0% end-tidal concentration), or narcotic-nitrous oxide anesthesia. Neuromuscular blockade was monitored by recording the electromyographic activity (Datex NMT) of the adductor pollicis muscle resulting from supramaximal stimulation of the ulnar nerve at 2 Hz for 2 s at 10-s intervals. Effective vecuronium infusion requirements averaged 1.5 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (mean ± SEM) during isoflurane-narcotic-nitrous oxide anesthesia, 1.9 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during halothane-narcotic-nitrous oxide anesthesia, and 2.4 ± 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during narcotic-nitrous oxide anesthesia. Infusion requirements significantly decreased after the first 30 min of infusion in the presence of both potent inhalation anesthetics, but did not change with time during narcotic-nitrous oxide anesthesia. There was no evidence of decreasing infusion requirements during prolonged vecuronium infusion (2.5 h). There was no difference in the rate of spontaneous or pharmacologically induced recovery between anesthetic groups. The mean recovery index (T_{25-75}) after termination of the infusion was 13.7 min.

(Anesth Analg 1991;73:33–8)

Because of its intermediate duration of action and noncumulative effects, vecuronium should be useful as a continuous infusion. Indeed, vecuronium has been administered as an infusion to children (1) and to adults (2–5) during narcotic-nitrous oxide anesthesia. Vecuronium infusion requirements (IRs) during narcotic-nitrous oxide anesthesia differ with age. It is likely, therefore, that the vecuronium IRs of children differ from those of adults during potent inhalation anesthesia as well. There are no published reports of vecuronium IR in children during anesthesia with halothane or isoflurane. It is to be expected that these potent inhalation anesthetics would increase the neuromuscular blocking effect of vecuronium and hence decrease IR (2,3). Therefore, we were interested in determining the infusion rate of vecuronium required to maintain a clinically effective state of neuromuscular blockade in children during narcotic-nitrous oxide anesthesia in the presence of halothane or isoflurane.

Methods

The study was approved by the Human Rights Committee of the Children's Hospital of Pittsburgh. Informed consent was obtained from a parent. Thirty-nine children (ASA status I and II) aged 2–10 yr were studied. All were undergoing low-to-moderate risk elective surgical procedures that required endotracheal intubation. No patient received aminoglycoside antibiotics, or antihistamines within 48 h of the study. Most patients received no premedication; three were given 0.1–0.2 mg/kg of diazepam orally or midazolam intramuscularly. The children were randomly assigned to one of three study groups: 15 patients received halothane-nitrous oxide, oxygen, and fentanyl (group H); 14 patients received isoflurane-nitrous oxide, oxygen, and fentanyl (group I); and 10 patients received nitrous oxide, oxygen, and fentanyl (group N).

In all patients, anesthesia was induced with nitrous oxide, oxygen, and a potent inhalation anes-

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Accepted for publication February 5, 1991.

Address correspondence to Dr. Woelfel, Department of Anesthesiology, Children's Hospital of Pittsburgh, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213-2583.

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0003-2999/91/$3.50

Table 1. Demographic Data

	Age (mo)	Height (cm)	Weight (kg)	BSA (m^2)
Group H	69.5 ± 9.2	116.1 ± 4.6	21.8 ± 2.3	0.84 ± 0.06
(*n* = 15)	(26.8–130.7)	(90.0–140.0)	(11.5–37.0)	(0.5–1.2)
Group I	54.4 ± 5.9	106.9 ± 3.4	18.2 ± 1.2	0.76 ± 0.04
(*n* = 14)	(22.6–101.4)	(91.0–133.0)	(13.6–30.0)	(0.6–1.1)
Group N	55.6 ± 9.7	100.5 ± 4.6	17.5 ± 1.8	0.70 ± 0.05
(*n* = 10)	(22.5–113.8)	(88.0–124.0)	(12.4–29.0)	(0.6–1.0)

BSA, body surface area.
Values are expressed as mean ± SEM, with the range given in parentheses.
There were no statistically significant differences between anesthetic groups.

thetic. A venous catheter was inserted, and atropine (10 μg/kg) was given intravenously to all patients before tracheal intubation. The inspired and end-tidal concentrations of halothane and isoflurane were monitored continuously with a Puritan Bennett infrared gas analyzer. In groups H and I, respectively, anesthesia was maintained with 70% nitrous oxide in oxygen and halothane (0.8% end-tidal concentration) or isoflurane (1.0% end-tidal concentration). Patients in groups H and I received 1–6 μg/kg of fentanyl as clinically indicated. In group N, thiopental (4–8 mg/kg) and midazolam (0.1 mg/kg) were administered intravenously, and the potent agent was discontinued. Anesthesia was maintained in group N with fentanyl (2.7–11.3 μg/kg) and 70% nitrous oxide in oxygen. Normal minute ventilation and body temperature (rectal or skin) were maintained intraoperatively in all patients.

After induction of general anesthesia, the ulnar nerve was stimulated supramaximally at the wrist with repetitive trains-of-four (2 Hz for 2 s at 10-s intervals) through surface electrodes. The evoked compound electromyogram (EMG) of thumb adduction was recorded by a Datex neuromuscular transmission monitor.

End-tidal concentrations of anesthetic were allowed to stabilize for 10–15 min, and a stable baseline EMG was obtained for at least 3 min before the administration of vecuronium. In group N the end-tidal halothane or isoflurane concentration was 0% for 5–10 min before administration of vecuronium. An intravenous bolus of 60 μg/kg of vecuronium was injected. The maximum neuromuscular blocking effect was recorded, and the trachea was intubated. When the first response (T_1) of the EMG signal returned to 5% of baseline (T_5), an infusion of vecuronium in lactated Ringer's solution (200 μg/mL) was administered at 1.5–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with an infusion pump. The infusion was titrated to produce 89%–99% neuromuscular blockade for as long as required by the surgical procedure (range, 36–149 min). For each patient the infusion rate of vecuronium required to achieve 89%–99% blockade was calculated and recorded at 3-min intervals. Data from 3-min periods during which neuromuscular blockade was outside the 89%–99% range were not included in the analyses. For each patient the mean effective IR was calculated for three periods: the first 30 min of infusion; the duration of infusion excluding the first 30 min, and the total duration of infusion. The time from termination of the infusion to 5% (T_5), 10% (T_{10}), 25% (T_{25}), 50% (T_{50}), and 75% (T_{75}) of baseline and the time until $T_{4/1} \geq 75\%$ were noted. Recovery was referenced to the final EMG baseline (T_1 when $T_4 = T_1$). End-tidal inhalation anesthetic concentration was maintained constant until $T_4 = T_1$. Twenty-five patients received 1 mg/kg edrophonium when T_1 was greater than T_{50}, and recovery was then monitored until recovery of neuromuscular function was complete.

Vecuronium IR was calculated on the basis of both weight ($\mu g \cdot kg^{-1} \cdot min^{-1}$) and body surface area (BSA) ($\mu g \cdot m^{-2} \cdot min^{-1}$). Standard errors are shown for all mean values. Analysis of variance and Tukey's test were used to assess the differences between groups. Paired *t*-tests were used to compare the IR before and after the first 30 min and the total IR. Differences were considered significant at $P < 0.05$.

Results

There was no statistical difference in age, height, weight, or BSA among the three groups of patients studied (Table 1).

There was no significant difference between anesthetic groups in time to onset of complete block after the initial bolus dose, or in T_5 after bolus administration of vecuronium (Table 2). The total IR for group H was 1.9 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (47.5 ± 3.4 $\mu g \cdot m^{-2} \cdot min^{-1}$), for group I 1.5 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (36.9 ± 2.4 $\mu g \cdot m^{-2} \cdot min^{-1}$), and for group N 2.4 ± 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (61.1 ± 7.5 $\mu g \cdot m^{-2} \cdot min^{-1}$). There was no significant difference between these values for groups H and I; however, the total IR was significantly greater for group N (Table 3). A significant decrease in IR was

Table 2. Onset and Initial Recovery Times From Bolus

	Onset time to 100% block (min)	Time to 5% neuromuscular transmission (T_5) (min)
Group H	2.7 ± 0.3 (1.8–4.3) (n = 10)	9.9 ± 1.3 (4.8–17.0) (n = 10)
Group I	2.2 ± 0.2 (1.5–2.8) (n = 7)	11.5 ± 1.1 (8.4–15.5) (n = 6)
Group N	2.4 ± 0.3 (1.5–3.3) (n = 6)	9.5 ± 1.0 (8.0–14.3) (n = 6)

Values are expressed as mean ± SEM, with range given in the first set of parentheses and the number given in the second set.

There were no statistically significant differences between groups.

observed after the first 30 min of infusion in groups H and I but not in group N (Figure 1) (Table 3).

The average duration of infusion administration in minutes was 86 ± 5 for group H, 98 ± 7 for group I, and 85 ± 12 for group N. The percentage of time that neuromuscular blockade was not maintained within the desired 89%–99% depression of function during the first 30 min of infusion administration averaged 22% ± 5% in group H, 26% ± 5% in group I, and 26% ± 8% in group N. In the first 30 min of administration of vecuronium nine patients had a period of 100% neuromuscular blockade. All other patients who did not have neuromuscular blockade in the desired range had less than 89% neuromuscular blockade. The percentage of time that neuromuscular blockade was outside the desired range after the first 30 min of infusion administration averaged 4% ± 1% in group H, 6% ± 3% in group I, and 4% ± 3% in group N. The coefficient of variation of the IR (standard deviation divided by mean) was similar for the potent inhalation agents (20%–25%) and greater in group N (40%).

After termination of the infusion, the time required for spontaneous recovery of neuromuscular transmission to T_{25} (n = 34) and the rate of recovery tended to be less in group N than in groups H and I, but the difference was not statistically significant (Table 4). In those patients (n = 25) who received edrophonium later than T_{50}, $T_{4/1}$ increased to 75% within 0.2–1.3 min. Those patients (n = 7) with infusion duration of greater than 2 h had recovery indices that were not statistically different from those in patients receiving infusions for approximately 1 h or less (n = 12). The recovery indices after infusions of short versus long duration were T_{10-25}: 4.9 ± 0.9 versus 4.7 ± 0.7 min; T_{25-50}: 6.3 ± 0.9 versus 6.5 ± 1.1 min; and T_{25-75}: 13.9 ± 1.9 versus 15.2 ± 5.6 min, respectively.

Neuromuscular function (T_1) when $T_4 = T_1$ was not always 100% of initial baseline. The final baseline of neuromuscular function averaged 90% ± 11%, 80% ± 9%, and 85% ± 10% of the initial baseline in group H, I, and N, respectively. When neuromuscular function during infusion was referenced to the final rather than the initial baseline, a paired t-test demonstrated no significant change in IR.

Discussion

The vecuronium IR that we observed during narcotic-nitrous oxide anesthesia in children 2–10 yr of age was similar to that reported by Meretoja (1). The IR in $\mu g \cdot kg^{-1} \cdot min^{-1}$ or in $\mu g \cdot m^{-2} \cdot min^{-1}$ for children 2–10 yr of age during narcotic-nitrous oxide anesthesia was greater than that of adults exposed to the same anesthetic (2–5). In a study by D'Hollander et al. involving 24 adults in three groups (i.e., 18–36 yr, 40–60 yr, and 63–85 yr) during narcotic-nitrous oxide anesthesia (5), average IR was less in the oldest group: 46.5, 45, and 29.5 $\mu g \cdot m^{-2} \cdot min^{-1}$, respectively (Figure 2). The increased IR of vecuronium in children compared with that in adults is similar in magnitude to that seen with mivacurium (6–8). The age-related difference in IR for atracurium appears to be somewhat less (9–11).

There also appears to be an age-related difference in IR for vecuronium during anesthesia with potent inhalation agents. In adults anesthetized with halothane (0.5% end-tidal concentration)-nitrous oxide, an average vecuronium IR of 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced a 90% depression of neuromuscular function (2). In adults anesthetized with isoflurane (1.2% end-tidal concentration)-nitrous oxide, an average vecuronium IR of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ also produced a 90% depression of neuromuscular function (3). It appears that the vecuronium IR in children aged 2–10 yr may be at least twice as great as that in adults in the presence of potent inhalation anesthesia as well as during narcotic-nitrous oxide anesthesia.

Other studies of the effects of anesthetic background on the infusion requirements for neuromuscular blocking drugs in children have not always found significant differences in potentiation between halothane and isoflurane (9), or halothane and narcotic (11) anesthesia. In this study the difference in average effective infusion rate of vecuronium 30 min after the beginning of infusion during halothane and isoflurane anesthesia was only 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The standard deviation was 0.39 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The ratio, δ/σ, is therefore less than 0.8. With 15 patients in each experimental group there would be about a 50% chance of demonstrating a difference between the two groups assuming an acceptable α error of 0.05 (12). More than 20 patients per experimental group

Table 3. Changing Vecuronium Infusion Requirements Over Time

Anesthetic	Total IR ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	IR during min 1–30 ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	IR during min > 30 ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
Group H	1.9 ± 0.1^{a}	2.2 ± 0.1^{b}	$1.8 \pm 0.1^{b,c}$
(n = 15)	(1.2–2.7)	(1.3–3.2)	(1.2–2.4)
Group I	1.5 ± 0.1^{d}	1.8 ± 0.1^{e}	$1.5 \pm 0.1^{e,f}$
(n = 14)	(1.0–2.2)	(1.2–2.6)	(0.9–2.2)
Group N	$2.4 \pm 0.3^{a,d}$	2.3 ± 0.3	$2.4 \pm 0.3^{c,f}$
(n = 10)	(1.5–4.0)	(0.7–4.0)	(1.6–4.0)

Values are expressed as mean ± SEM, with the range given in parentheses.
IR, infusion requirement.
[a–f] Statistically significant difference in infusion rate at $P < 0.05$ is indicated by like letters (paired t-test for the comparison of IR before and after minute 30 of infusion).

would be necessary to expect close to an 80% chance of finding a significant difference between the IR during exposure to 0.8% end-tidal halothane and 1.0% end-tidal isoflurane.

In our study, variability in vecuronium IR was noted primarily during the first 30 min of the infusion (Figures 1*A*, *B*, and *C*). During potent inhalation anesthesia in this study, there was a significant decrease in IR of approximately 20% after the first 30 min of infusion that was not observed during narcotic-nitrous oxide anesthesia. The infusion rate was frequently adjusted before a constant IR and constant degree of paralysis were attained. A greater IR early in the administration of vecuronium was noted during narcotic-nitrous oxide anesthesia by D'Hollander et al. (5). Swen et al. found no difference in time to steady-state IR for vecuronium during nitrous oxide-fentanyl or nitrous oxide-halothane anesthesia (2). Swen et al. did not comment on the degree of variability in vecuronium IR before the attainment of a constant IR and constant effect.

During the first 30 min of infusion administration of vecuronium, neuromuscular function was outside the desired range about 25% of the time. Therefore the effective IR estimated during this period may well differ from the amount infused during more efficient titration. If the infusions had been titrated most appropriately, allowing inclusion of more data during the first 30 min of infusion in the calculation of IR during that time, the calculated IR would have been even greater. After the first 30 min of infusion administration, neuromuscular function was outside the desired range about 5% of the time. Thus, the effective IR estimated during this period is more likely to be easily reproducible.

A change in IR of neuromuscular blocking drug with continued infusion and anesthetic administration could be due to changing concentrations of the neuromuscular blocker at the effect site (presumably the neuromuscular junction) or to changing concen-

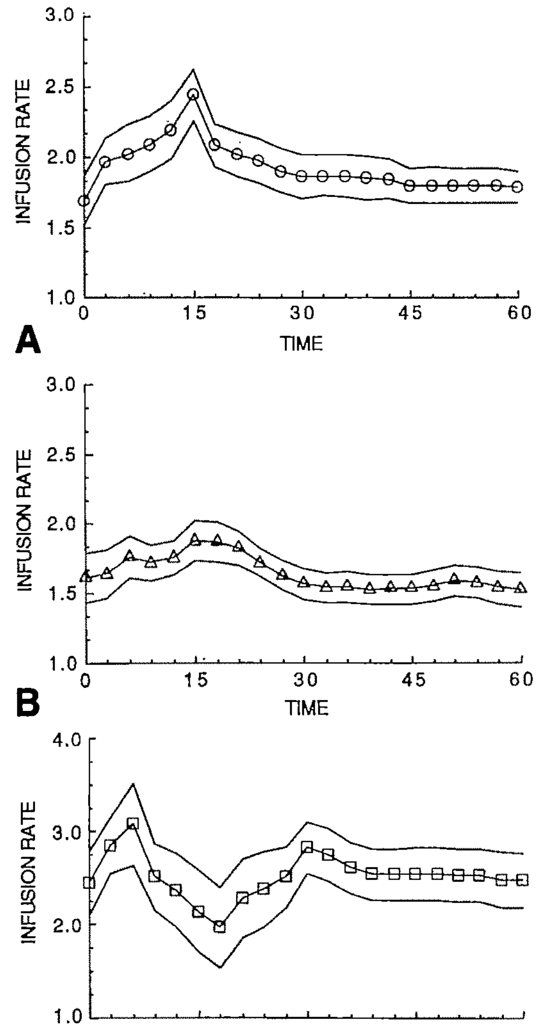

Figure 1. Relationship of mean IR ± SEM ($\mu g \cdot kg^{-1} \cdot min^{-1}$) over time for each group: halothane-nitrous oxide (○), isoflurane-nitrous oxide (△), and narcotic-nitrous oxide (□). Infusion requirements are significantly decreased after the first 30 min in groups H and I. The range is greater in group N. The total IR is greater in group N.

Table 4. Recovery Data After Vecuronium Infusion

	T_{25} (min)	T_{10-25} (min)	T_{25-50} (min)	T_{25-75} (min)
Group H	9.1 ± 1.2 (5.0–22.7) (*n* = 15)	4.7 ± 0.7 (1.0–11.4) (*n* = 13)	5.7 ± 0.7 (3.1–8.7) (*n* = 8)	15.0 ± 2.7 (6.8–18.2) (*n* = 4)
Group I	8.1 ± 1.0 (4.0–15.0) (*n* = 13)	5.0 ± 0.5 (3.0–7.0) (*n* = 8)	6.2 ± 0.7 (2.8–10.6) (*n* = 12)	13.7 ± 1.8 (6.8–26.3) (*n* = 10)
Group N	6.8 ± 1.0 (4.5–9.2) (*n* = 6)	4.1 ± 0.4 (2.0–5.0) (*n* = 6)	3.7 ± 1.7 (2.0–5.3) (*n* = 2)	7.9 ± 3.9 (4.0–11.7) (*n* = 2)

Values are expressed as mean ± SEM, with range given in the first set of parentheses and number given in the second.
There were no statistically significant differences between groups.

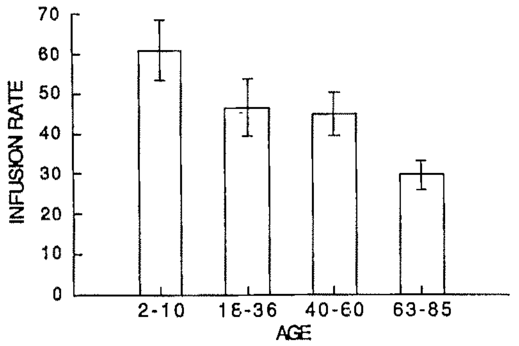

Figure 2. Relationship between age (yr) and IR ± SEM ($\mu g \cdot m^{-2} \cdot min^{-1}$). Data in adults are from a study by D'Hollander et al. (5). The anesthetic is narcotic-nitrous oxide.

trations of the potentiating anesthetic. If delayed equilibration at the effect site with potentiating inhalation anesthetics were the major factor responsible for the variability in vecuronium IR during the first 30 min of infusion, a similar degree of variability should be apparent in studies of other drugs administered during similar types of anesthesia. Such an observation has not been reported. In a study of atracurium IR that used stimulus parameters identical to those of this study, similar EMG monitoring of neuromuscular function, and identical administration of halothane (0.8% end-tidal concentration) and isoflurane (1.0% end-tidal concentration), halothane and isoflurane significantly potentiated atracurium-induced neuromuscular blockade by about 30% (9). Differences in variability of IR with anesthetic background early in the administration of the infusion were not mentioned (9). In a similar study with mivacurium, IR in the first 12 min of infusion was greater during nitrous oxide-fentanyl anesthesia than during nitrous oxide-halothane anesthesia (6).

The children in our study recovered more rapidly from vecuronium infusion than did adults observed by others. In a study during narcotic-nitrous oxide anesthesia, the shortest recovery indices (T_{10-25} of 8.4 ± 1.2 min and T_{25-75} of 16.2 ± 4.0 min) were observed in the youngest patients (age range, 18–36 yr) (5). The same recovery indices appear shorter (4.1 ± 0.4 min and 7.9 ± 3.9 min, respectively) in our children during narcotic-nitrous oxide anesthesia. During halothane (1.0% end-tidal concentration) anesthesia in adults, the recovery index (T_{25-75}) was 23 ± 8 min (13). In our current study of children, the average T_{25-75} during halothane anesthesia was 15 ± 2.7 min. Both these observations and the greater IR in children relative to adults could be due to more rapid removal of vecuronium from the effect site in children relative to adults.

From a clinical standpoint, this study demonstrates that halothane-narcotic-nitrous oxide (0.8% end-tidal concentration) and isoflurane-narcotic-nitrous oxide (1.0% end-tidal concentration) anesthesia reduce vecuronium IR in children to a similar extent compared with narcotic-nitrous oxide anesthesia. After a bolus of vecuronium that will produce about 95% neuromuscular blockade, 2.0–2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of vecuronium is a useful initial infusion rate in children 2–10 yr of age under all types of anesthesia, whereas this initial rate is likely to decrease to 1.5–1.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after the first 30 min in children anesthetized with halothane or isoflurane and nitrous oxide. The mean IR can serve only as a starting point for the infusion of vecuronium, because a wide range of steady effective IR was observed in these patients.

After the termination of the infusion, spontaneous recovery of neuromuscular transmission occurs rapidly. Alternatively, reversal of blockade is easily achieved with edrophonium. Children (2–10 yr) have an increased vecuronium IR compared with adults under all types of anesthesia; they also have a faster spontaneous rate of recovery after the infusion is terminated.

We thank Wayne DellaMaestra for his significant contribution to data analysis.

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Distribution, Elimination, and Action of Vecuronium in the Elderly

Cynthia A. Lien, MD, Richard S. Matteo, MD, Eugene Ornstein, PhD, MD,
Arthur E. Schwartz, MD, and Jaime Diaz

Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York

The effects of age on the pharmacokinetics and pharmacodynamics of vecuronium in eight elderly patients aged 72–86 yr and eight younger adults aged 26–48 yr undergoing elective surgical procedures under nitrous oxide-fentanyl anesthesia were studied. Vecuronium (0.1 mg/kg) was given as an intravenous bolus, and the ulnar nerve was stimulated with a square-wave impulse of 0.2-ms duration. The response to stimulation at a frequency of 0.1 Hz was measured and recorded with a force displacement transducer applied to the thumb. Spontaneous recovery was significantly longer in elderly patients than in younger patients (50% recovery time, 97.1 ± 29 vs 39.8 ± 14 min, mean ± SD; recovery index [25%–75%], 49.4 ± 11 vs 15.0 ± 8 min). In addition, in elderly patients elimination half-life of vecuronium was significantly prolonged (125 ± 55 vs 78 ± 21 min, $P = 0.04$) and plasma clearance reduced (2.6 ± 0.6 vs 5.6 ± 3.2 $\mathrm{mL \cdot kg^{-1} \cdot min^{-1}}$, $P = 0.049$). The prolonged duration of action of vecuronium in the elderly surgical patients thus appears to be secondary to altered pharmacokinetics consistent with an age-related decrease in renal and hepatic functions.

(Anesth Analg 1991;73:39–42)

There have been conflicting reports in the elderly of the pharmacokinetics and pharmacodynamics of vecuronium, a nondepolarizing muscle relaxant of intermediate duration of action. D'Hollander et al. (1) in a study of patients older than 60 yr and two groups of younger patients found that spontaneous recovery indexes from 10% to 25% and from 25% to 75% twitch height were significantly longer in the older patients. Although they did not study kinetics, their results suggested decreased elimination of the drug in elderly patients. Rupp et al. (2,3) examined the pharmacokinetics and pharmacodynamics of vecuronium in elderly patients given an infusion of vecuronium that was discontinued once twitch tension had decreased to 20%–30% of control. Elderly patients (>70 yr old) had significantly decreased plasma clearances and volumes of distribution, whereas elimination half-life of vecuronium and recovery index (25%–75% of control) were not significantly different, when compared with that of their younger counterparts. They concluded that "healthy elderly patients do not appear to represent a population distinctly different from younger adults in their pharmacokinetic/pharmacodynamic response."

The present study was undertaken to obtain additional data on the distribution, elimination, and action of vecuronium in elderly patients with the intention of clarifying and reconciling the conflicting reports of vecuronium in elderly surgical patients.

Methods

After institutional review board approval, informed consent was obtained from eight young (aged 26–48 yr) and eight elderly (aged 72–86 yr) ASA physical status I–III patients undergoing elective neurosurgical procedures. Patients with hepatic, renal, or neuromuscular disease and those taking medications known to affect neuromuscular transmission were eliminated from the study.

Patients were premedicated with oral diazepam (10 mg) and with intramuscular glycopyrolate (0.2 mg) at the discretion of their anesthesiologists. In the operating room, electrocardiograms, pulse oximeters, blood pressure cuffs, capnographs, and esophageal temperature probes were used for monitoring. After preoxygenation, anesthesia was induced with fentanyl (4–7 μg/kg), midazolam (20–100 μg/kg), droperidol (10–40 μg/kg), and thiopental (2–5 mg/kg).

Accepted for publication February 20, 1991.

Address correspondence to Dr. Lien, Department of Anesthesiology, The New York Hospital, Cornell Medical Center, 525 East 68th Street, New York, NY 10021.

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0003-2999/91/$3.50

Ventilation with nitrous oxide and oxygen (70%:30%) was controlled using an anesthesia face mask.

The ulnar nerve was stimulated at the wrist through surface electrodes with a supramaximal square-wave impulse of 0.2-ms duration. The stimulus was delivered at a frequency of 0.1 Hz from a Grass S8 stimulator in conjunction with a Grass stimulation isolation unit. Response to stimulation was measured and recorded with a force displacement transducer (Grass model FT-10) applied to the thumb.

Once the baseline adduction response of the thumb was obtained, patients were given vecuronium (0.1 mg/kg) as an intravenous bolus. After vecuronium was administered, the trachea was intubated and mechanical ventilation was instituted and adjusted to maintain normocarbia. Anesthesia was maintained with 70% nitrous oxide, 30% oxygen, and a continuous fentanyl infusion of 2–3 $\mu g \cdot kg^{-1} \cdot h^{-1}$. After the twitch response had returned to at least 90% of the baseline, atracurium was given if further muscle relaxation was required. Esophageal temperature was maintained between 34.8 and 36.6°C with warming blankets.

Heparinized blood samples were obtained from an indwelling arterial catheter just before the administration of vecuronium and 1, 3, 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 300, and 360 min after its administration. These samples were immediately placed in tubes containing 1 M sodium phosphate buffer at a pH of 4.0. The ratio of blood to buffer was 4:1. Additional samples were drawn between the timed kinetic samples as warranted by return of twitch response. The plasma was separated and frozen. At a later date, the samples were prepared for analysis using an anion exchange column (Bakerbond specially made by J.T. Baker, Phillipsburg, N.J.). Vecuronium concentration was determined by the spectrofluorometric method described by Kersten et al. (4). The maximum sensitivity of this method is 25 ng/mL with the coefficients of variation no more than 6%.

The times to 5%, 25%, 50%, and 75% recovery of twitch height were recorded, and the 5%–25% and 25%–75% recovery indexes were determined. The plasma concentration versus time-course curves for each patient were fit to both biexponential and triexponential equations, using weighted nonlinear least-squares regression analysis (5). A weighting function of $1/x_i^2$ was used. The best fit for the data was then determined by the method of Boxenbaum et al. (6). Pharmacokinetic values were calculated using standard methods for bolus intravenous injection of a drug. The female:male ratios were compared using χ^2 analysis. The recovery indices, recovery times, and pharmacokinetic values were compared between the elderly and control groups using Student's two-tailed *t*-tests for unpaired data. The concentration-time data points were compared in the two groups using repeated measures analysis of variance. The threshold for statistical significance was $P < 0.05$.

Table 1. Demographics and Intraoperative Conditions of the Study Populations

	Young	Elderly	*P*
Sex (F:M)	3:5	4:4	0.642
Weight (kg)	81 ± 14	71 ± 14	0.200
Temperature (°C)	35.9 ± 0.4	35.7 ± 0.7	0.536
$ETco_2$ (mm Hg)	29 ± 2	29 ± 7	0.855

$ETco_2$, end-tidal carbon dioxide tension.
Values are mean ± SD.

Table 2. Recovery Times and Recovery Indices

	Young	Elderly	*P*
Time to recovery (min)			
5%	21.1 ± 7.3	47.3 ± 15.5	0.001
25%	32.0 ± 11.6	73.8 ± 24.4	0.001
50%	39.8 ± 13.5	97.1 ± 29.3	0.0002
75%	47.9 ± 15.6	123.1 ± 33.3	0.0001
Recovery index (min)			
5%–25%	10.7 ± 5.2	27.8 ± 18.0	0.032
25%–75%	15.0 ± 8.0	49.4 ± 11.4	0.0001

Values are mean ± SD.

Results

The age of the young control group was 41 ± 7 yr (mean ± SD) and that of the elderly patients 77 ± 4 yr. There were no significant differences between the two study populations in terms of sex, weight, intraoperative $ETco_2$, and temperature (Table 1). The return of twitch and the recovery indexes were significantly longer in the elderly than in the younger patients (Table 2).

Figure 1 demonstrates the plasma time-concentration data (± SD) for each of the groups. At 60 min, the plasma concentration of vecuronium in the elderly group of patients became significantly greater than the plasma concentration in the control group. The statistical significance of this difference continued throughout the remainder of the study.

Plasma decay curves for both groups were best described by biexponential equations. In the elderly, elimination half-life of vecuronium was significantly prolonged and clearance of vecuronium was decreased (Table 3).

Discussion

The distribution and elimination of drugs in the elderly may be altered by a multitude of physiologic changes that accompany the aging process. These

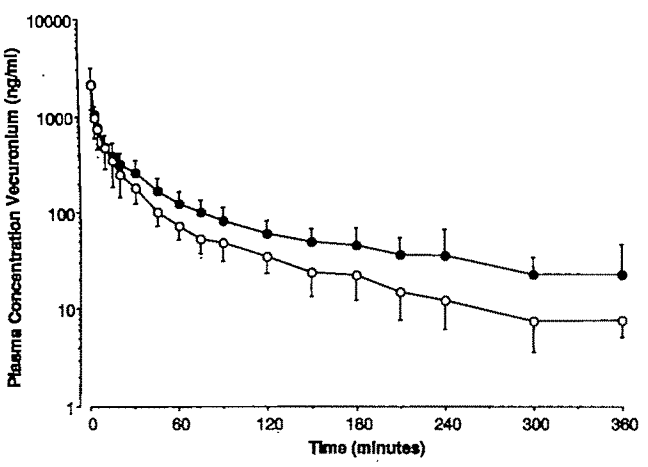

Figure 1. Plasma concentration versus time-course in elderly (●-●) and in younger (O-O) patients after a single intravenous dose (0.1 mg/kg) of vecuronium. Values are mean ± SD; $n = 8$ in each group except at 360 min where $n = 5$ for elderly and $n = 6$ for younger patients.

Table 3. Pharmacokinetic Variables

Variables	Young	Elderly	P
$t_{1/2}$ elim (min)	78 ± 21	125 ± 55	0.040
Clp ($mL \cdot kg^{-1} \cdot min^{-1}$)	5.6 ± 3.2	2.6 ± 0.6	0.049
Vi (L/kg)	0.08 ± 0.02	0.08 ± 0.01	0.474
Vd area (L/kg)	0.49 ± 0.02	0.44 ± 0.01	0.335

$t_{1/2}$ elim, half-life of elimination; Clp, plasma clearance; Vi, initial volume of distribution; Vd area, volume of distribution.

Values are mean ± SD.

changes include decreases in lean body mass, in total body water, in glomerular filtration and renal blood flow, in splanchnic blood flow, and in serum albumin levels, and increases in fat. The long-acting nondepolarizing muscle relaxants pancuronium (7,8), metocurine (9), and *d*-tubocurarine (9) have prolonged durations of action in the elderly related to decreased elimination of these drugs through the kidneys. The elimination of vecuronium is, in addition to being effected by the kidneys, highly dependent on hepatic clearance; 40% of a vecuronium dose is eliminated unchanged in the bile within 24 h after its administration (10). As aging is associated with reductions of both splanchnic and renal blood flows (11,12), one would expect duration of action and the elimination of vecuronium also to be prolonged in the elderly.

Previous studies (1–3) have yielded conflicting results as to the pharmacodynamics of vecuronium in the elderly. D'Hollander et al. (1) studied recovery rates in patients older than 60 yr and compared them with results obtained in two younger groups of patients after the discontinuation of a continuous infusion of vecuronium adjusted to maintain twitch height constant at 10% of baseline for at least 90 min. They found that the recovery indices of both 10%–25% and 25%–75% were significantly prolonged in the group greater than 60 yr of age. Although they did not study kinetics, their results suggested decreased elimination of the drug in elderly patients. Rupp et al. (2,3) looked at both the pharmacokinetics and pharmacodynamics of vecuronium in the elderly. Their patients were given a continuous infusion of 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of vecuronium until the twitch tension was 20%–30% of control, at which point the infusion was terminated. Elderly patients (>70 yr old) had significantly decreased plasma clearances and volumes of distribution, whereas elimination half-life of vecuronium and recovery indices (25%–75% of control) were not significantly different from younger counterparts. It was concluded that "healthy elderly patients do not appear to represent a population distinctly different from younger adults in their pharmacokinetic/pharmacodynamic response." In contrast, the data presented in this study demonstrate prolonged recovery after an intravenous bolus of vecuronium, prolonged elimination half-life, and decreased clearance of vecuronium in the elderly.

Although in the study of Rupp et al. (2,3), the reported kinetic and dynamic data obtained in younger patients (25%–75% recovery index, 10 ± 1 min; elimination half-life, 70 ± 20 min; clearance, 5.2 ± 0.8 $mL \cdot kg^{-1} \cdot min^{-1}$; volume of distribution at steady state (Vd_{ss}), 244 ± 38 mL/kg) are not that dissimilar from values reported in this study, there are significant differences in the data obtained for the elderly patients, including a recovery index of 11 ± 1 min and an elimination half-life of 58 ± 10 min versus the values of 49.4 ± 11.4 and 125 ± 55 min obtained in this study, respectively. There are several reasons that the results of this study may differ from those of Rupp et al. Differences in anesthetic technique (nitrous oxide-halothane used by Rupp's group as opposed to nitrous oxide-fentanyl used in this study) is a possible reason. A nitrous oxide-halothane anesthetic may cause prolonged recovery times when compared with the return of twitch during a nitrous oxide-narcotic technique. As the recovery indices in Rupp's study are appreciably less than those in this study, it is unlikely that anesthetic technique accounts for the differences observed. In addition, as the elderly patients in both Rupp's and our study received the same anesthetic as their respective controls, the anesthetic agents should not be a factor within each study.

A major difference between the two studies is the method of vecuronium administration. In this study, 0.1 mg/kg of vecuronium was given as an intravenous bolus. This dose was sufficient to cause complete muscle paralysis in all patients, and twitch did not return to 5% of the control value for 21.1 ± 7.3 min (mean ± SD) in the younger patients and 47.3 ±

15.5 min in the elderly. Because return of twitch clearly occurred during the elimination phase of the drug in our study, a decrease of plasma clearance of vecuronium should produce a delay in recovery time. This indeed is what was observed in the elderly patients in this study. In contrast, Rupp et al. infused vecuronium until the twitch was 20%–30% of the control value, stopped the infusion, and began his measurements. No indication was given of the total dose of muscle relaxant given to the patients. The elderly may have received less relaxant to achieve the desired end point. If the elderly patients received a smaller dose of vecuronium than the younger controls, the possibility exists that Rupp et al. were looking at recovery during the redistribution phase rather than during the elimination phase. This could account for their surprising report that the clearance of vecuronium is significantly decreased in elderly patients although there is no difference in recovery time between the younger and elderly patients. In support of this theory, Fisher and Rosen (13), using computer simulation, determined the effect of the relaxant dose on the duration of action of the relaxants. They clearly demonstrated that when a moderate dose of vecuronium (40 μg/kg) is administered, recovery occurs during the drug's distribution phase. As drug dose is increased, recovery of twitch occurs further into the elimination phase.

These data can also be used to explain the finding of D'Hollander et al. after a prolonged infusion of vecuronium (90 min at a steady-state 90% depression of twitch response). In that study, elderly patients required a significantly longer period of time for return of twitch height from 25% to 75% of baseline value. Clearly in D'Hollander's study, a large vecuronium dose was administered to the patients and a return of twitch response occurred during the elimination phase. Although D'Hollander et al. did not measure drug concentration nor calculate pharmacokinetic values, their results are clearly compatible with a decreased plasma clearance of vecuronium in elderly patients.

Studies by Bell et al. (14) and O'Hara et al. (15) demonstrated no differences in the dose-response relationships of vecuronium in the elderly and in the young. In both studies, a single-dose methodology was used to compare the potency of the muscle relaxant in these two groups. Their results, because of study design, reflect the distribution of the muscle relaxant rather than its elimination. The distribution of a drug is, in turn, closely related to its volume of distribution. That there is no significant difference in the volumes of distribution between the elderly and the young patients in this study provides a clear pharmacokinetic explanation of why both Bell et al. and O'Hara et al. reported no differences in the dose-response relationship of vecuronium between the two age groups.

Our finding that the action of vecuronium is prolonged in the elderly is clearly in agreement with that of D'Hollander et al. The prolongation of vecuronium action appears to be secondary to decreased drug elimination in older patients, consistent with age-associated decreases in hepatic and renal blood flows. The results of this study suggest that anesthesiologists should expect the action of vecuronium to be prolonged in the elderly surgical patient and emphasize the need to administer carefully and to monitor closely the effects of neuromuscular blocking agents in these patients.

The authors acknowledge with gratitude the aid of Dr. Michael J. Avram, Assistant Professor, Department of Anesthesia, Northwestern University Medical School, in establishing the spectrofluorometric method of analysis of vecuronium in our laboratory.

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Continuous Measurement of Intraarterial pHa, $Paco_2$, and Pao_2 in the Operating Room

Steven J. Barker, PhD, MD, and John Hyatt, BS

Department of Anesthesiology, University of California, Irvine, Orange, California

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Miniaturized sensors based upon the principles of optical fluorescence can measure the pH, Pco_2, and Po_2 of liquid or gas media. A prototype of a three-component fiberoptic sensor has been developed for intraarterial application by CDI, 3M Health Care, Irvine, California. We report the first study of this continuous intraarterial monitor in patients undergoing surgical procedures under general anesthesia. Fourteen patients participated in the study. The fiberoptic sensor was calibrated before insertion and then passed through an existing 18-gauge radial artery cannula. Blood samples were drawn at frequent intervals through the same cannula for in vitro blood gas analysis. For each of the 87 arterial blood gas samples obtained, the in vitro values of pHa, $Paco_2$, and Pao_2 were compared with simultaneous readings from the fiberoptic sensor. For pHa, the mean error (error = fiberoptic value minus in vitro value) or "bias" of the fiberoptic data was −0.032 and the standard deviation of error or "precision" was 0.042. For $Paco_2$, the bias was −3.8 mm Hg and the precision was 4.7 mm Hg. For Pao_2, the bias was −9.0 mm Hg and the precision was 23.3 mm Hg. For Pao_2 values less than 175 mm Hg, the bias was −8.5 mm Hg and the precision was 8.3 mm Hg. Expressed in terms of percentage errors, the bias ± precision values were −11.5% ± 13.3% for $Paco_2$, and −6.2% ± 10.0% for Pao_2. The duration of the surgical procedures ranged from 1.6 to 8 h with an average of 4.2 h. Although further refinements in accuracy are needed, particularly for $Paco_2$, this study demonstrates both the feasibility and clinical utility of continuous intraoperative three-component blood gas monitoring.

(Anesth Analg 1991;73:43–8)

Intermittent sampling of arterial blood for in vitro blood gas analysis does not provide continuous data and is subject to variable delays between sampling and receiving results. Because blood gas values can change very rapidly in the operating room, there has been a strong incentive to develop continuous intraarterial monitoring of pHa, $Paco_2$, and Pao_2. The first approach to this problem was the miniaturization of electrochemical sensors based on the same principles as the laboratory blood gas analyzer. Leland Clark's polarographic oxygen electrode has been miniaturized and inserted through arterial cannulas by several investigators (1–3). Electrochemical pH and Pco_2 electrodes have also been miniaturized for intravascular placement (4). Although these methods showed promise, calibration drift was a consistent problem and there was little hope of monitoring all three variables simultaneously through a single arterial cannula.

Fiberoptic blood gas sensors are based on the phenomenon of luminescence, which is the emission of light from certain molecules whose electrons have been excited into energy levels above the ground state. In photoluminescence (fluorescence), incident light provides the energy required to excite these molecules to the higher energy levels. When the excited electrons return to their ground states, they reemit light of a longer wavelength than that of the stimulating light. In some fluorescent dyes, this process is inhibited by the presence of oxygen. Although this phenomenon of fluorescence quenching by oxygen was first reported in the 1930s (5), the first optical Po_2 sensor based on this principle was developed by Lubbers and Opitz in 1975 (6). These authors referred to their optical Po_2 sensor as an "optode," a term that has endured. The measurement of fluorescence can also be utilized to sense pH and Pco_2. The Pco_2 sensors use a pH-sensitive dye encapsulated in a bicarbonate solution, which is in turn covered by a CO_2-permeable membrane. This is the same indirect CO_2 measurement principle used by the Severinghaus-Stow carbon dioxide electrode in laboratory blood gas analyzers.

The simplicity and potential for miniaturization of the optode make it an ideal candidate for an intravas-

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Accepted for publication February 12, 1991.

Address correspondence to Dr. Barker, University of California, Irvine, Department of Anesthesiology, Orange, CA 92668.

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0003-2999/91/$3.50

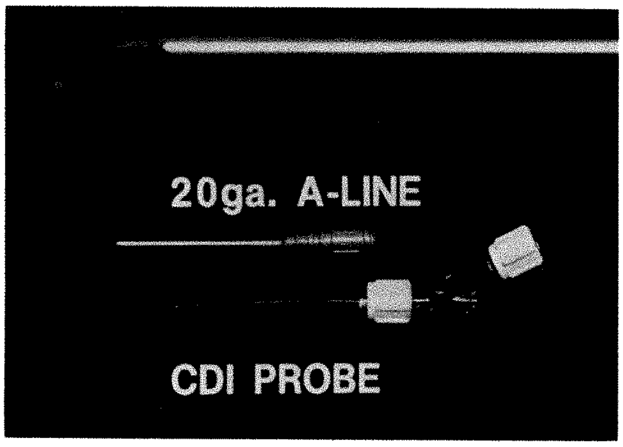

Figure 1. The CDI, 3M Health Care three-component intraarterial optode sensor. External diameter is 0.061 cm (0.024 in.). A 20-gauge, 4-cm-long intravenous cannula is shown for comparison.

cular blood gas sensor. Peterson et al. developed an oxygen optode that was inserted intraarterially in sheep in 1984 (7). Further studies of smaller intraarterial optodes in animals were reported by Barker et al. (8) and by Shapiro et al. (9). An operating room study of a 0.5-mm-diameter oxygen optode was reported by Barker et al. in 1987 (10), and a volunteer study of a three-component system was reported by Mahutte et al. in 1990 (11).

The three-component fiberoptic prototype system used in the present study was developed by CDI, 3M Health Care, Irvine, California (12,13). The sensor, shown in Figure 1, contains three optical fibers to measure pH, P_{CO_2}, and P_{O_2}, and a thermocouple to determine blood temperature. The composite sensor is 0.6 mm (0.024 in.) in diameter and fits easily through a 20-gauge cannula. Heparin is covalently bonded to the probe to reduce thrombogenicity. The pH optode utilizes the dye hydroxypyrene trisulfonic acid, which fluoresces at a wavelength of 520 nm. The P_{CO_2} sensor uses a similar dye encapsulated in a gas-permeable matrix with a bicarbonate buffer to provide indirect P_{CO_2} sensing. The oxygen optode uses a proprietary oxygen-quenched fluorescent dye that emits light at a wavelength above 400 nm. The sensor is connected via a fiberoptic cable to the patient interface module, which is in turn connected to the analyzer and display modules. The analyzer module contains the xenon light source for excitation of the photoluminescent dyes in the sensor, an optical collimator, and a filter wheel. The patient interface module contains the solid state photodetector, which converts the photoluminescence into an electrical signal. This analog electrical signal is digitized and transmitted to the analyzer module, where the microprocessor unit applies the appropriate temperature-dependent calibration and calculates pH, P_{CO_2}, and P_{O_2}. The resulting blood gas values can be displayed either at the patient's radial artery blood temperature or corrected to a temperature of 37°C. The fiberoptic sensor is calibrated before insertion into the arterial cannula by a tonometric calibration instrument. This device automatically performs a two-point calibration of all three optodes, using precisely controlled oxygen and carbon dioxide mixtures. (The first calibration gas contains 2.8% CO_2 and 5.5% O_2; the second contains 8.4% CO_2 and 14% O_2.) This preinsertion calibration requires approximately 15 min. An in vivo recalibration can also be performed at the user's discretion, using data from an in vitro blood gas analyzer as a standard. In the study described below, there were no in vivo recalibrations, and 37°C blood gas values were used throughout.

Methods

Fourteen patients undergoing surgical procedures under general anesthesia participated in this study, which had been approved by the University Human Subjects Review Committee. A variety of general surgical, orthopedic, and neurosurgical procedures were included, and all patients required arterial cannulation for surgical or anesthetic reasons. No patients were systemically heparinized. An 18-gauge, 4.4-cm-long cannula (Critikon, Inc.) was inserted into the distal radial artery of each patient. The CDI System 1000 blood gas sensor was calibrated before insertion as described above. No calibration changes were made during this study once the optode sensor was inserted into the arterial cannula. The tip of the sensor was slightly recessed behind the distal end of the arterial cannula. After insertion of the optode, the cannula was connected to an arterial pressure transducer (Spectramed). A continuous infusion of heparinized saline (2 U/mL) was flushed through the cannula at a rate of 3 mL/h. Arterial pressure waveforms were recorded on analog strip-chart before and after insertion of the optode.

An adjustable passive compliance device was inserted into the arterial line tubing at the pressure transducer. The device consists of a 2-cm-diameter plastic diaphragm whose spring constant is adjustable by means of a variable-volume air cavity on one side. The opposite side of the diaphragm is in contact with the fluid in the arterial line tubing. This additional compliance allows oscillatory flow of blood at the cannula tip to ensure that the optode sensor is continuously exposed to blood. However, it does not degrade the fidelity of the pressure tracing enough to cause errors in systolic or diastolic pressure measurements. After insertion of the optode, the compliance device was adjusted manually until the dicrotic notch of the pressure tracing began to flatten out. Once this adjustment was made at the time of optode insertion, it was not changed during the remainder of the case. Without this additional compliance in the system, the optode blood gas measurements would be contaminated by the saline flush solution.

Blood samples were aspirated from the arterial cannula at frequent intervals using anaerobic technique. Each 2-mL heparinized sample was analyzed for pH, Pco_2, and Po_2 using standardized electrodes (IL-813 Blood Gas Analyzer). The blood gas analyzer was calibrated daily using reference standards. The in vitro blood gas results (corrected to 37°C) were compared with simultaneous corresponding 37°C values from the CDI intraarterial blood gas sensor. Blood gas specimens were obtained every 20 min during stable conditions and more frequently during anesthetic induction and other unstable periods. A total of 87 samples were analyzed in the 14 participating patients.

This study is a methods comparison—that is, a new method of measurement is compared with an established method or "gold standard." Some previous methods comparisons have reported only correlation coefficients and linear regressions as statistics showing degree of agreement between the two methods. Correlation and regression are indicators of the association between two variables, not the degree of agreement between two methods of measurement. Several authors have suggested that the mean and standard deviation of the differences between the two methods of measurement provide a much better assessment of agreement (14,15). None of these statistics provides complete information regarding the agreement between two methods without plots of the raw data or "scattergrams." Accordingly, we provide the raw data in graph form as well as the means and standard deviations of the errors (error = fiberoptic value minus in vitro value), also called "bias" and "precision." We also present the means and standard deviations of the fractional or percentage errors, which we call "% bias" and "% precision." If x and y are simultaneous values measured by the in vitro and fiberoptic methods, $y - x$ is the error and $(y - x)/[(y + x)/2]$ is the fractional error. Because pH is a logarithmic variable, the % bias and % precision analysis is not appropriate for pH.

Results

Figure 2 shows fiberoptic intraarterial oxygen tension (Poo_2) and carbon dioxide tension ($Poco_2$) plotted as functions of time during a thoracotomy that required one-lung ventilation. Sampled arterial blood gas data are indicated on the figure by + symbols. The course of the hypoxemia and concomitant hypercarbia that occurred during this case is followed in detail by the optode tracing. Note that the sampled arterial blood gas data completely missed the period of significant hypoxemia occurring at approximately 12:20 PM. The intraarterial tracing not only captured this episode, but the trend of Poo_2 for the previous 30 min should have warned the clinicians of the impending problem. This case displayed an extreme range of both Poo_2 and $Poco_2$: the Poo_2 varied from 50 to more than 500 mm Hg and the $Poco_2$ varied from 30 to more than 70 mm Hg.

Eighty-seven arterial blood gas samples were obtained in 14 patients participating in the study. Figure 3 shows a comparison of the optode blood gas values (pHo, $Poco_2$, Poo_2) with the simultaneous blood gas analyzer values (pHa, $Paco_2$, Pao_2) in scattergram format. Linear regression lines and lines of identity are shown. Figure 4 shows the data in "bias-plot" format—that is, the error (optode value minus in vitro value) is plotted as a function of the in vitro value for each variable. A statistical comparison of the optode and blood gas analyzer values is shown in Table 1. For each of the three variables, the table gives the bias (mean error), precision (standard deviation of error), the % bias and % precision [mean and standard deviation

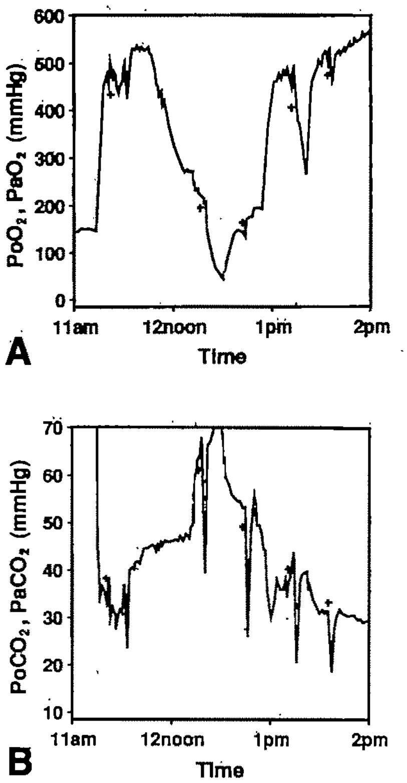

Figure 2: Continuous tracings of Poo_2 (A) and $Poco_2$ (B) versus time during a thoracotomy requiring one-lung ventilation. Sequential in vitro blood gas values are shown by + signs. Episode of hypoxemia and hypercarbia at 12:20 PM is shown in detail in optode tracing (*solid line*), but is missed by sequential blood gas analyses (+). Trend of falling Poo_2 and rising $Poco_2$ is seen well before hypoxemia or any changes in Spo_2 occurred.

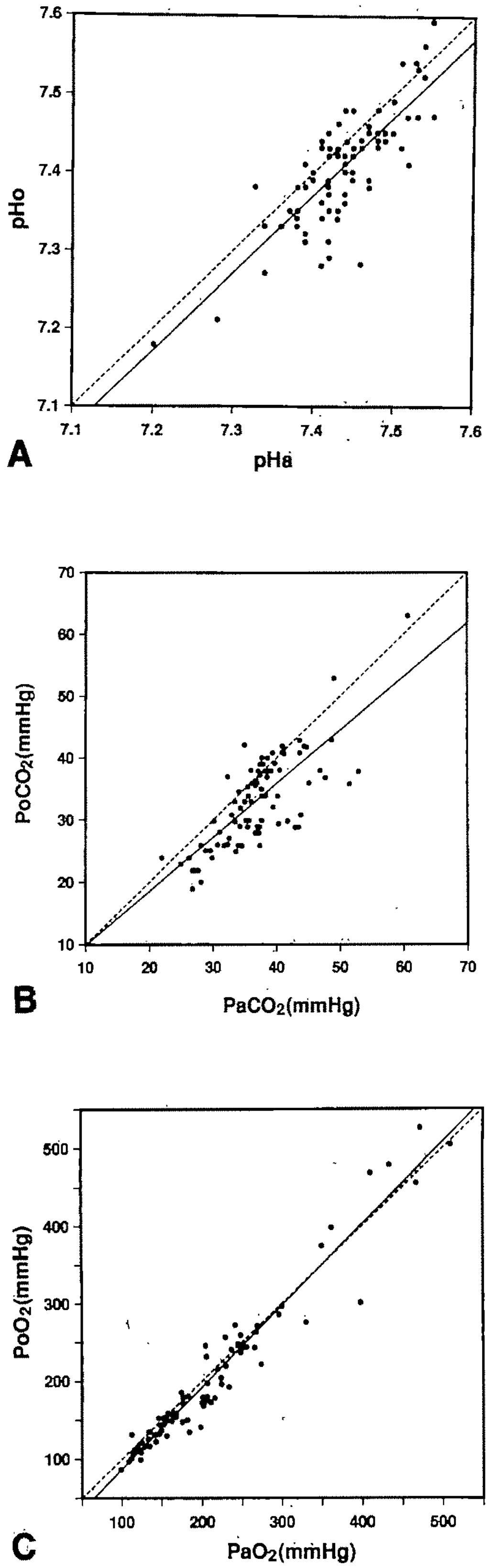

Figure 3. Scatter plots showing optode values (pHo, Poco$_2$, Poo$_2$) and simultaneous in vitro analyzer values (pHa, Paco$_2$, Pao$_2$); 14 patients, $n = 87$. Line of identity: - - - - - -; linear regression: ——.

of $2(y - x)/(y + x)$], and the linear regression slope, intercept, and standard error of the estimate. Judging from the oxygen data of Figures 3C and 4C, the accuracy of the optode appears greatest in the lower part of the Pao$_2$ range. Therefore, Table 1 also includes statistics for Pao$_2$ values less than 175 mm Hg. The standard errors of the estimate and the precision, both of which indicate the degree of random error or "scatter" of the data, are much less for this lower Pao$_2$ range.

Strip-chart tracings of arterial blood pressure were recorded before and after insertion of the optode and adjustment of the passive compliance device in each patient. The presence of the optode in the arterial cannula had no measurable effect on the accuracy of systolic and diastolic pressure measurements when an automated sphygmomanometer (Datascope model 2000) was used as a standard. The ease of withdrawing blood samples from the arterial cannula was also not noticeably affected. The cannula was promptly flushed with heparinized saline immediately after withdrawing each blood sample, and gross clot formation within the cannula or on the optical fiber was not observed. The mean duration of the surgical procedures in this study was 4.2 h; the longest procedure lasted 8 h.

Discussion

This is the first reported clinical study of a three-component intraarterial optode in the operating room. One study has been reported from the intensive care unit, which is a very different clinical setting and does not provide the same range of blood gas variables that is seen in the operating room (16). Results in healthy volunteers have also been reported, but these cannot be expected to predict the behavior of optode sensors in the operating room (11).

The in vitro performance of the CDI, 3M Health Care fiberoptic blood gas sensor is comparable to that of commercial blood gas analyzers (12,13). In fact, its accuracy in vitro is within the standards of the College of American Pathologists for blood gas analyzer accuracy: ±0.03 for pH, ±7.5% for Pco$_2$, and ±7.5% for Po$_2$. Initial studies in animals also yielded very promising results (12). However, early unpublished studies in critically ill patients showed poor or inconsistent accuracy. An unpublished study in the intensive care unit by Shapiro revealed problems with oxygen tension accuracy. Mahutte et al. investigated possible reasons for this discrepancy in their human volunteer experiments (11). They obtained their best results with the optode tip retracted slightly into the arterial cannula, the same geometry used in the present study. They obtained bias ± precision values of -0.003 ± 0.02 for pH, 0.77 ± 2.44 mm Hg for Pco$_2$, and -2.9 ± 25.4 mm Hg for Po$_2$. Mahutte's

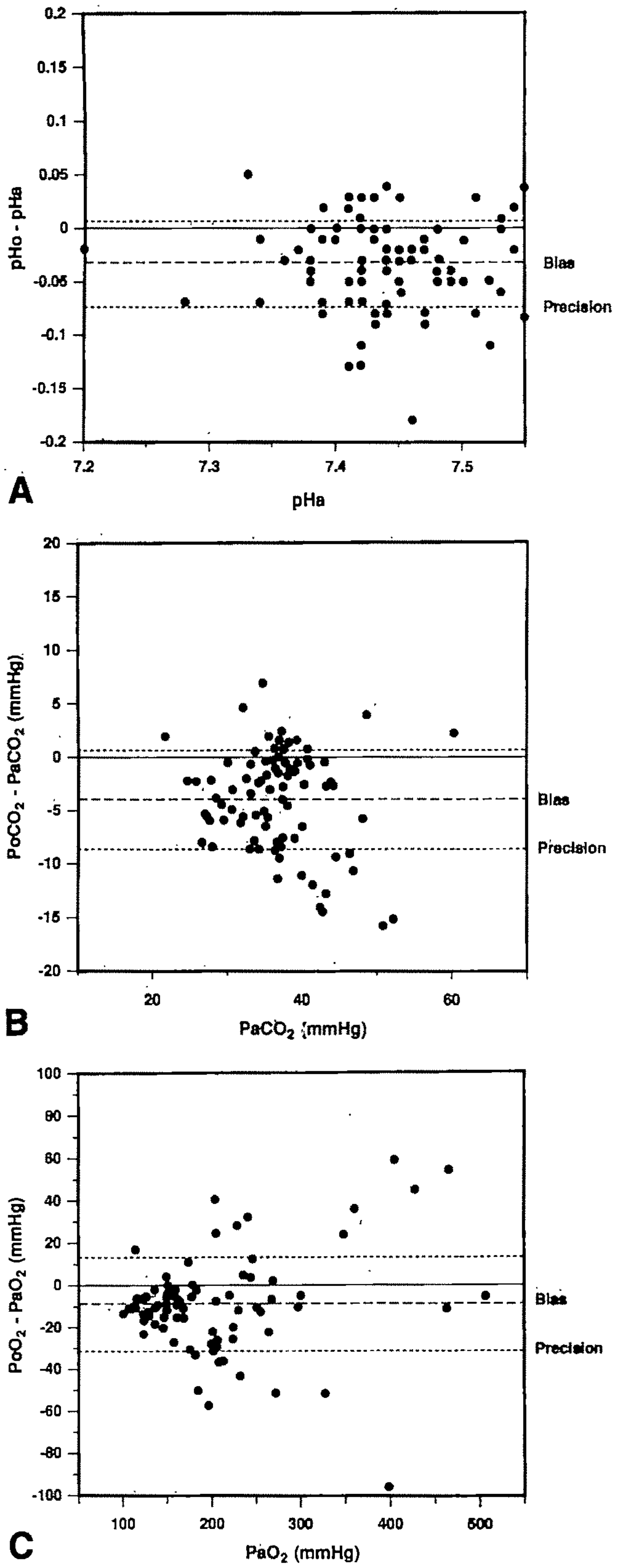

Figure 4. Bias plots showing values of error (pHo − pHa, $Poco_2$ − $Paco_2$, Poo_2 − Pao_2) plotted versus in vitro analyzer values (pHa, $Paco_2$, Pao_2); 14 patients, *n* = 87. Bias or mean error: - - - - - ; ± precision: . . . . . .

data were obtained in healthy, awake volunteer subjects, whereas our data come from anesthetized surgical patients. The accuracies indicated in Table 1 are the best obtained to date in a clinical study of a three-component intraarterial optode system. Although not yet within the standards of the College of American Pathologists, the accuracy exhibited here is certainly approaching a clinically useful range. Table 1 and Figures 3C and 4C show that the accuracy for Pao_2 measurement is greatest at low oxygen tensions, an important feature. A 15% error may be unimportant at a Pao_2 of 500 mm Hg; it is unacceptable at a Pao_2 of 50 mm Hg.

All three blood gas variables tend to be slightly underestimated by the intraarterial optode, as shown by the negative bias values in Table 1. For pH and $Paco_2$, this may represent contamination from the heparinized saline flush solution coming in contact with the retracted optode tip. This is a disadvantage of the retracted probe geometry. On the other hand, fiberoptic sensors protruding beyond the tip of the arterial cannula have been subject to blood clotting and arterial wall effects (11). The passive compliance device described above allows oscillatory flow of blood at the tip of the sensor, and without it the contaminating effect of the saline flush is far worse.

In our study we used an 18-gauge, 4-cm-long radial artery cannula. Mahutte et al. (11) and other investigators using the CDI system have generally used 20-gauge arterial cannulas. The 18-gauge cannula has an internal diameter of 0.0940 cm compared with 0.0838 cm for the 20-gauge cannula. This is only a 12% difference in internal diameter. However, when we subtract the cross-sectional area of the 0.0610-cm-diameter fiberoptic sensor from the cross section of the cannula, this difference becomes significant. The remaining cross-sectional area for the 18-gauge cannula is 0.0161 cm^2, whereas for the 20-gauge cannula it is 0.0104 cm^2. Thus the cross section of the residual lumen is 55% greater for the 18-gauge cannula. Because the recessed fiberoptic sensor is dependent on blood washing across it in an oscillatory flow, this difference in the lumen cross section becomes very significant. Furthermore, the heparinized saline flush solution is generally supplied at a constant-volume flow rate, in this case 3 mL/h. For a given volume flow, the flush fluid velocity in the vicinity of the sensor tip will be 55% greater for the 20-gauge cannula than for the 18-gauge cannula.

We have shown in this study that the three-component intraarterial optode blood gas sensor is clinically useful in the operating room when inserted through an 18-gauge radial artery cannula. During the course of these experiments, a significant venous air embolism was detected by the intraarterial sensor before the anesthesiologist was alerted by other mon-

Table 1. Statistical Comparison of Intraarterial Optode Values (pHo, $Poco_2$, Poo_2) With Simultaneous Blood-Gas Analyzer Values (pHa, $Paco_2$, Pao_2) (n = 87)

	Blood-gas variable			
	pH	Pco_2	Po_2	Po_2 (Pao_2 < 175 mm Hg)
Linear regression				
Slope	0.987	0.873	1.053	1.026
Intercept	0.0648	0.944	−19.9	−12.0
Standard error of estimation	0.0428	4.63	23.1	8.52
Bias	−0.0323	−3.77	−9.03	−8.46
Precision	0.0423	4.65	23.3	8.32
% Bias		−11.5%	−6.17%	−6.63%
% Precision		13.3%	9.99%	6.47%

A separate Po_2 comparison is shown for Pao_2 <175 mm Hg, n = 41. Bias and precision are mean ± SD of absolute error (error = fiberoptic value minus in vitro value); %bias and %precision are mean ± SD of percentage error.

itors, including the capnograph, central venous pressure transducer, pulse oximeter, and precordial Doppler stethoscope (17). In another case (Figure 2), impending hypoxemia occurring during one-lung ventilation was predicted by the optode before any changes were seen on the pulse oximeter. Although further improvements in accuracy are still needed, continuous arterial blood gas monitoring in the operating room is feasible and can provide significant improvements in the care of critically ill patients.

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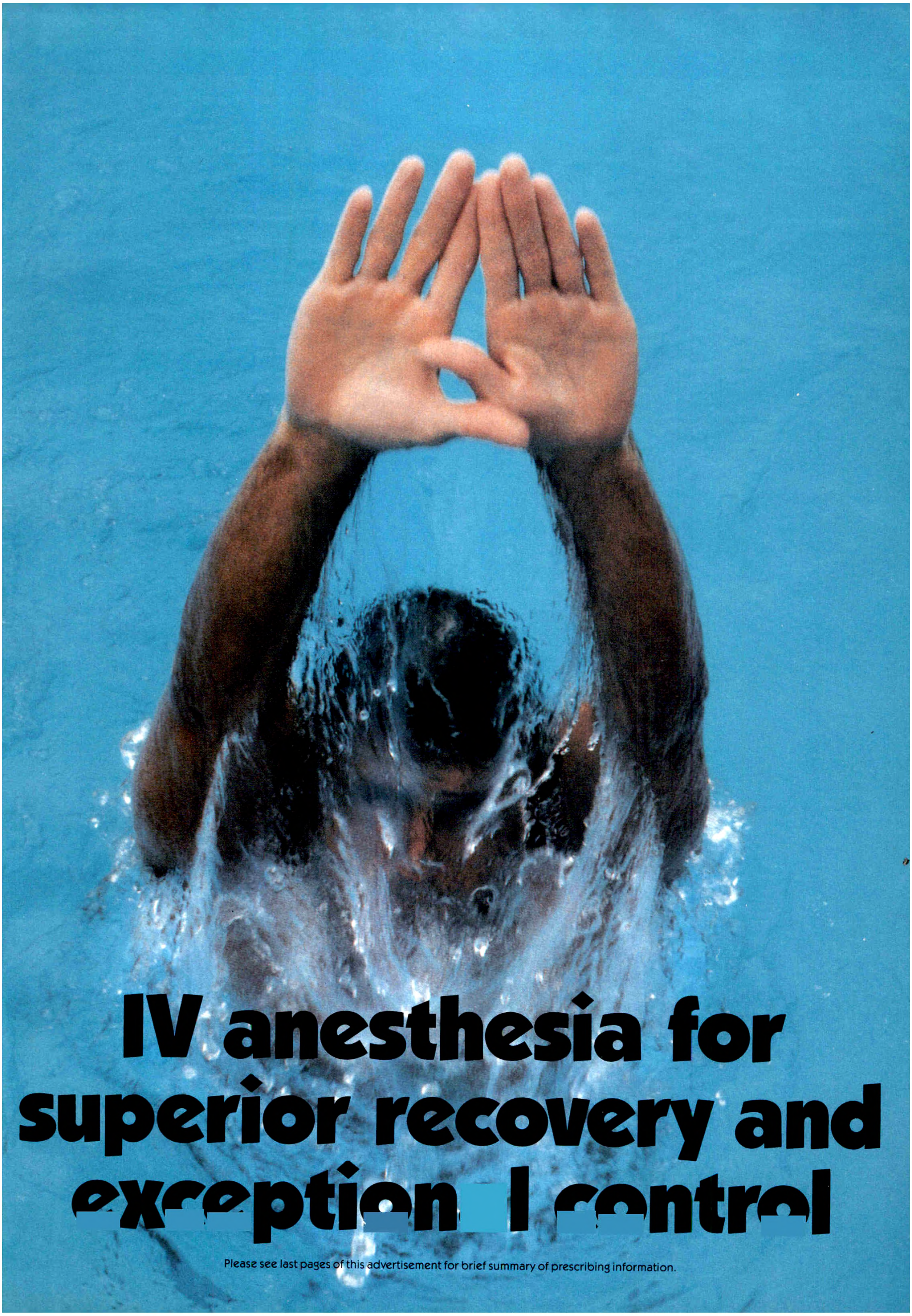

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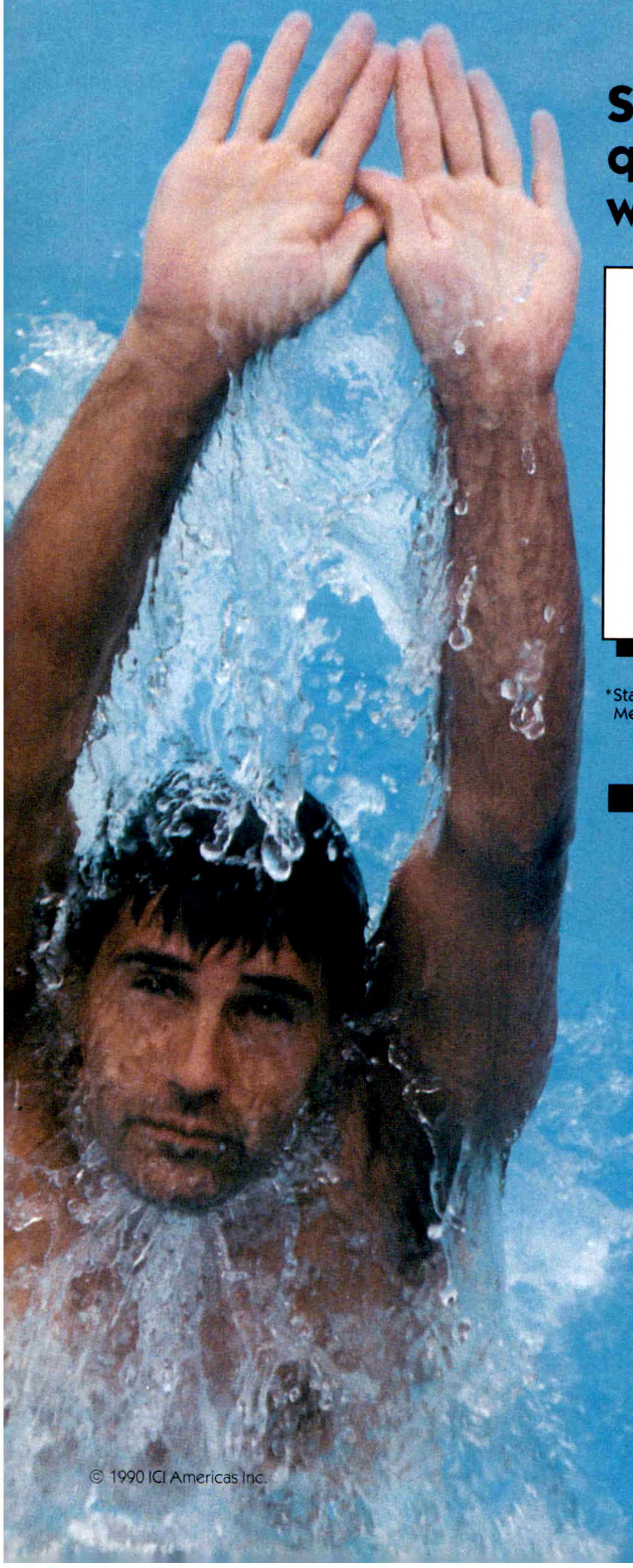
Superior
exceptional



Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

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recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

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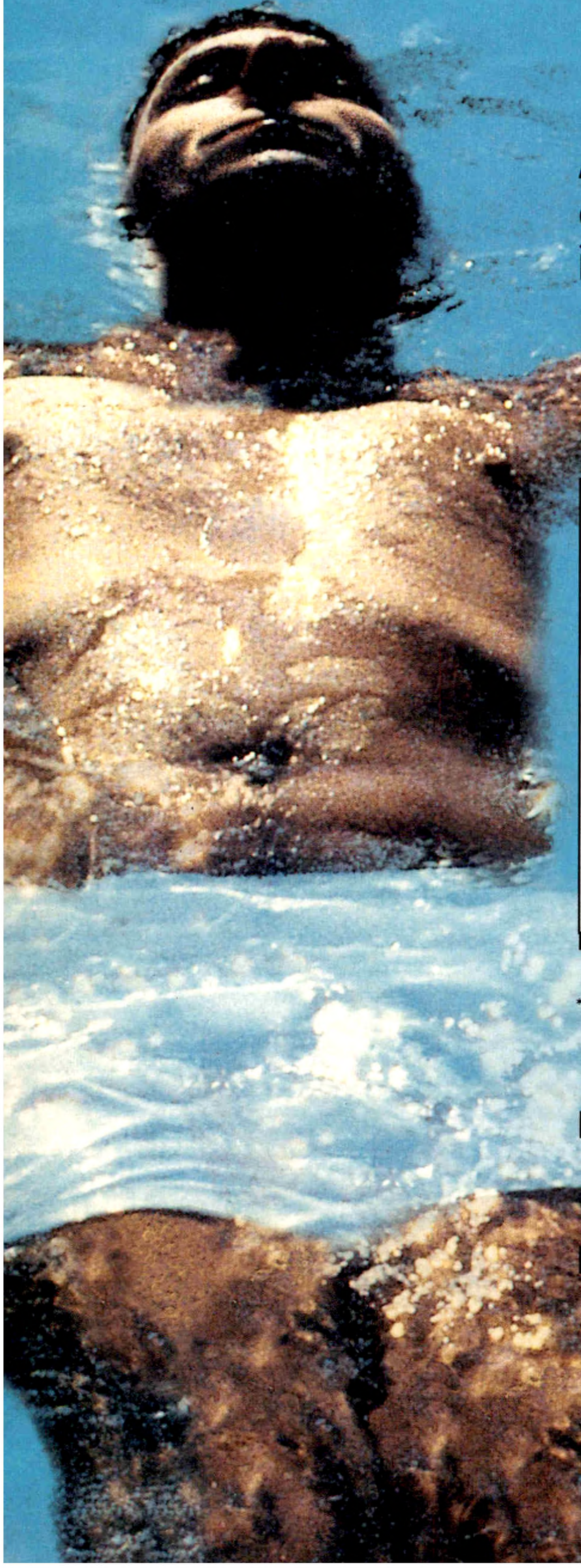
For induction and maintenance

DIPRIVAN®

INJECTION

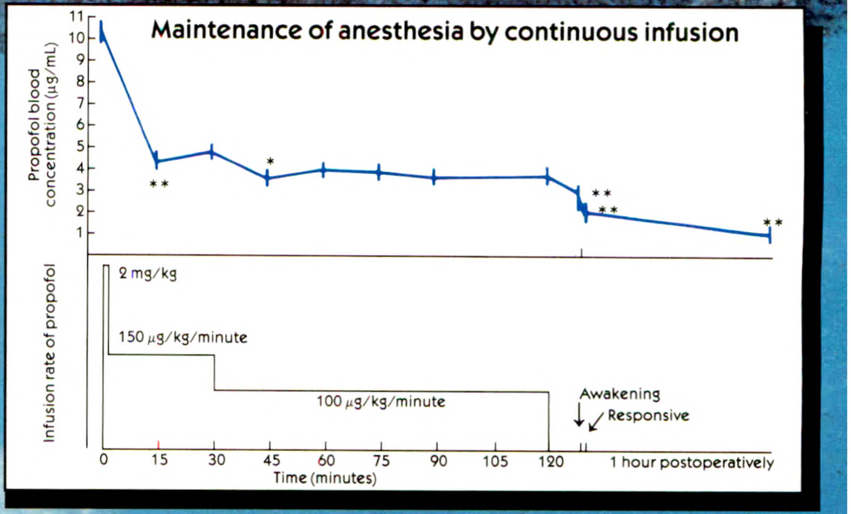
propofol

Superior exceptional



Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration


Maintenance of anesthesia by continuous infusion

—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recovery and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.

[†] Induction dose requirements may be reduced.

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For induction and maintenance

DIPRIVAN®

INJECTION

propofol

For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

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DIPRIVAN®

INJECTION
10 mg/mL
propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)
INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.) **CONTRAINDICATIONS:** When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components. **WARNINGS:** DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.** DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known. **Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.) PRECAUTIONS: General:** A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home. Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae. Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Clinical features of anaphylaxis, which may include bronchospasm, erythema, and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear. DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli. **Information for Patients:** Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia. **Drug Interactions:** The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. **Nursing Mothers:** DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. **Pediatric Use:** DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. **Neurosurgical Anesthesia:** Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures. **ADVERSE REACTIONS:** Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. **Incidence Greater than 1% – All events regardless of causality, derived from clinical trials. Body as a Whole:** Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/ Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing. Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater. **Incidence Less than 1% – Causal Relationship Probable** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*) **Body as a Whole:** Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing.

Injection Site: Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.* **Incidence Less than 1% – Causal Relationship Unknown** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*) **Cardiovascular:** Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, Myocardial ischemia. **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine. **DRUG ABUSE AND DEPENDENCE:** None known. **OVERDOSAGE:** To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids, and administering pressor agents and/or anticholinergic agents. The intravenous LD_{50} values are 53 mg/kg in mice and 42 mg/kg in rats. **DOSAGE AND ADMINISTRATION: Induction:** Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients, and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.) Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction. **Maintenance:** Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections. When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps, or volumetric pumps be used to provide controlled infusion rates. **Continuous Infusion:** DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating, and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five-minute period, other means such as a narcotic, barbiturate, vasodilator, or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times. **Intermittent Bolus:** Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	**DOSAGE AND ADMINISTRATION**
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic, and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic, and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration. **Dilution Prior to Administration:** When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.) **Administration Into a Running IV Catheter:** Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter: 5% Dextrose Injection, USP; Lactated Ringers Injection, USP; Lactated Ringers and 5% Dextrose Injection; 5% Dextrose and 0.45% Sodium Chloride Injection, USP; 5% Dextrose and 0.2% Sodium Chloride Injection, USP. **Handling Procedures:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if there is evidence of separation of the phases of the emulsion. Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When using vials with volumetric infusion devices insert sterile vent spike through rubber stopper and immediately connect IV line. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only, and any unused portions of DIPRIVAN Injection, reservoirs, IV lines, or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure. Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness. *Aseptic Techinque* for Handling DIPRIVAN Injection Ampules:* • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask, and hair cover. • Disinfect neck surface of ampule using 70% isopropyl alcohol. Swab neck of ampule by wiping in one direction and let dry. • Protect fingers and hands by using sterile gauze when opening the ampule. • Withdraw DIPRIVAN Injection into a sterile syringe. • Immediately replace needle cap and discard ampule. • Label syringe with appropriate information, including date, time, and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the surgical procedure or within 6 hours – whichever occurs sooner. *Aseptic Technique* for Handling DIPRIVAN Injection Vials (and for Use With Volumetric Infusion Devices):* • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask, and hair cover. • Remove metal cap from vial. • Disinfect rubber stopper of vial using 70% isopropyl alcohol. Wipe in one direction and let dry. • Insert sterile vent spike through rubber stopper and remove luer cap. • Connect a sterile syringe(s) to vent spike and withdraw entire contents; (Or when using volumetric infustion devices, aseptically connect IV line to vent spike). • Immediately cap syringe with sterile closure(s) and discard vial and vent spike. • Label syringe(s) (or vial when using volumetric infusion devices) with appropriate information, including date, time, and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the surgical procedure or within 6 hours – whichever occurs sooner.

*These techniques are not intended to preempt more stringent, established institutional guidelines for the aseptic handling and administration of sterile parenteral drug products. **HOW SUPPLIED:** DIPRIVAN Injection is available in ready to use 20 mL ampules and 50 mL infusion vials containing 10 mg/mL of propofol.
20 mL ampules (NDC 0038-0290-20) 50 mL infusion vials (NDC 0038-0290-50)
Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

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Anesthesia and Analgesia

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Neuromuscular blocking agents for the ICU: How do they compare?

	TRACRIUM	vecuronium	pancuronium
Good cardiovascular profile in surgical patients?	**YES**	**YES**	**NO** (vagolytic)[1]
Elimination half-life (based on single-dose kinetics)	**20 minutes**[2] (approximate)	**65 to 75 minutes**[3]	**89 to 161 minutes**[1]
Nonhepatic/non-renal mode of elimination…	**YES**	**NO**	**NO**
…unaltered by renal or hepatic dysfunction?	**YES**[2,6]*	**NO** significantly prolonged[3-6]*	**NO**[7]* doubled[1]
Rapid recovery after infusion even in patients with renal failure?	**YES** 47 to 105 minutes in five renal failure patients after 15-37-hr. infusion[6]	**NO** 6 to 37 hours in six renal failure patients after 7-32-hr. infusion[6]	**Infusion not recommended**[7]
Ready-to-use convenience?	**YES**	**NO** requires reconstitution	**YES**

TRACRIUM® *INJECTION*

(atracurium besylate)

Uniquely suited for infusion in the ICU

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* As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of metabolites following long-term (days to weeks) administration.

Please see brief summary of prescribing information on the next page.

TRACRIUM® *INJECTION*
(atracurium besylate)

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of $\geq$ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses $\leq$ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

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1. Package insert, Pavulon® (pancuronium bromide).
2. Package insert, Tracrium® Injection (atracurium besylate).
3. Package insert, Norcuron® (vecuronium bromide).
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Clinical and Metabolic Responses to Different Types of Premedication

Olli A. Kirvelä, MD, and Jussi H. Kanto, MD

Department of Anaesthesiology and Clinical Pharmacology, Turku University Hospital, Turku, Finland

Clinical and metabolic responses to three types of premedication were studied in ASA physical status I patients given any one of the following: (a) 0.5 mg of atropine and 50 mg of meperidine given intramuscularly plus an oral placebo tablet ($n = 14$), (b) 10 mg of oral diazepam and an intramuscular placebo (2 mL NaCl, concentration = 0.9) ($n = 14$), or (c) oral and intramuscular placebo ($n = 14$). Based both on subjective estimates (tiredness, fear, anxiety, dryness of mouth) and, especially, on metabolic responses (energy expenditure, oxygen consumption), oral diazepam appears to be superior to the combination of an opiate (meperidine) plus an anticholinergic (atropine). Atropine plus meperidine significantly increased energy expenditure above predicted values (2061 ± 365 vs 1714 ± 361 kcal/24 h, $P = 0.004$), calculated using the Harris–Benedict equation, based on sex, weight, height, and age, as well as increased oxygen consumption above levels seen with diazepam premedication (160 ± 29 vs 137 ± 17 $\mathrm{mL \cdot min^{-1} \cdot m^{-2}}$). These findings indicate an iatrogenic stress factor induced by premedication with atropine plus meperidine.

(Anesth Analg 1991;73:49–53)

Benzodiazepines, opiates, barbiturates, and histamine antagonists as well as anticholinergic agents often have been advocated as preoperative medication to control fear and anxiety and to eliminate or suppress the stress reaction to anesthesia and operation (1–3). The relationships between self-reported assessments of acute preoperative anxiety and several biochemical and physiologic indicators of stress reaction have been evaluated in many studies (4–9), but the metabolic effects of different types of premedication have not been as well studied. Indirect calorimetry has been used to measure the metabolic needs and changes in various patient populations (10), but the equipment involved is difficult to use and too bulky for everyday use in the operating room. The introduction of compact and easy-to-use metabolic monitors (11,12) offers an accurate and noninvasive way to measure the metabolic state of patients even in the operating room. In the present work, we compared oral diazepam, intramuscular atropine plus meperidine, and placebo with respect to differences in preoperative clinical and metabolic responses.

Methods

Forty-two ASA physical status I patients scheduled for hand surgery under axillary block were studied (Table 1). Admitted to the hospital only for the operation, none received any medication. The study was approved by the Ethics Committee of Turku University Hospital and written informed consent was obtained from each patient.

The patients were randomly allocated to receive one of three premedications: (a) group 1 were given 0.5 mg of atropine and 50 mg of meperidine intramuscularly plus an oral placebo tablet, (b) group 2 were given 10 mg of oral diazepam (tablet form) plus an intramuscular placebo (2 mL of NaCl, concentration = 0.9), and (c) group 3 received both oral and intramuscular placebos. There were 14 patients in each group, and the study was conducted in a double-blind fashion.

The patients were admitted to the hospital the day before the operation. No hypnotic medication was given in the evening. After fasting overnight, the patients received their premedication at least 30 min before they were transferred to the operating room. The patients remained resting in the supine position after premedication. On arrival in the operating room, the patients were placed in a quiet corner of the recovery room where they remained for the entire study period. Continuous monitoring of the electrocardiogram and heart rate (HR), together with non-

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Accepted for publication February 27, 1991.

Address correspondence to Dr. Kirvelä, Department of Anaesthesiology, University of Turku, Kiinamyllynkatu 4-8, SF-20520, Turku, Finland.

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Table 1. Patient Characteristics

	Sex		Age (yr)	Height (cm)	Weight (kg)
	F	M			
Group 1 (atropine + meperidine)	4	10	40 ± 13	174 ± 7	78 ± 14
Group 2 (diazepam)	2	12	40 ± 15	175 ± 9	80 ± 10
Group 3 (placebo)	3	11	43 ± 13	176 ± 9	82 ± 22

Values are mean ± SD.

Table 2. Subjectively Estimated Tiredness, Anxiety, Fear, and Dryness of Mouth

	Tiredness	Anxiety	Fear	Dryness of mouth
Group 1 (atropine + meperidine)	30 (17–75)^a	25 (10–75)	23 (10–60)	50 (15–75)^f
Group 2 (diazepam)	30 (15–75)^b	17 (1–65)^d	17 (1–65)	1 (1–60)^g
Group 3 (placebo)	13 (1–30)^c	30 (10–75)^e	28 (10–75)	1 (1–50)^h

$a > c$, $F = 0.001$; $b > c$, $P = 0.003$; $f > g$ and h, $P = 0.0001$; $e > d$, $P = 0.007$.

Tiredness, as millimeters on a 100-mm-long ungraded visual analog scale: 0 = fully alert, 100 = asleep; anxiety and fear, 0 = not at all, 100 = worst possible; dryness of mouth, 0 = normal, 100 = intolerable.

All values are given as medians (range).

invasive recording of systolic (BPS) and diastolic (BPD) blood pressures (Datascope Accutor 3, Paramus, N.J.) at 5-min intervals, was started. Ten minutes after arrival, ungraded visual analog scales (VAS) were used to collect subjective data (13) concerning fear, anxiety, tiredness, and dryness of mouth (Table 2).

After the VAS evaluation, the metabolic measurements were started. Patients were resting in their bed undisturbed, and the lights were dimmed. The entire measurement period for metabolic values was 30 min. The first 10 min and the remaining 20 min were analyzed separately to get a better understanding of the effects of premedication. A recently validated (11,12) portable metabolic cart system (Deltatrac, Datex/Instrumentarium, Helsinki, Finland) with good overall accuracy [2% ± 1% (12), 1.9% (11) for oxygen consumption (Vo_2) with a tidal volume of 500 mL] was used. The Deltatrac is an open-system indirect calorimetry device designed for measuring Vo_2 and carbon dioxide production (Vco_2). For the measurements, the patient's head is placed under a plastic cone (canopy) connected to the analyzer. The canopy is half-ellipsoidal and is made of 1-mm-thick transparent PVC plastic. It is provided with adapters for tubings and with a wide edge of soft plastic cloth to make the construction airtight under the head and around the neck of the patient. Minor leakages do not affect the results as they are directed inward due to the slight underpressure inside the canopy caused by the constant airflow (40 L/min) drawn through the canopy to the gas analyzers, and thus, all expired gases will be captured. The difference between inspired (Fio_2) (sampling at the entry valve of the canopy) and expired (Feo_2) oxygen fractions is measured with a fast-response paramagnetic differential oxygen sensor (OM-101, Datex/Instrumentarium, Helsinki, Finland). The expired CO_2 fraction (Feco_2) is measured with an infrared CO_2 sensor. A microcomputer controls a set of magnetic valves for the automatic control of the absolute Fio_2, the inspired carbon dioxide fraction (Fico_2), and gas analyzer baselines. Carbon dioxide consumption is calculated as the product of the constant flow and the fraction of CO_2 in the diluted expiratory flow:

$$\text{Vco}_2 = \text{Q} \times \text{Feco}_2,$$

where Q is the constant flow.

Oxygen consumption is calculated using the Haldane transformation:

$$\text{Vo}_2 = [\text{Q}/(1 - \text{Fio}_2)]$$
$$\times [\text{Fio}_2 - \text{Feo}_2 - \text{Fio}_2 \times (\text{Feco}_2 - \text{Fico}_2)],$$

where Feo_2 and Feco_2 are the fractions of oxygen and CO_2 in the mixed expiratory gas flowing through the monitor. Energy expenditure (EE) is calculated from the measured rates of Vo_2 and Vco_2:

$$\text{EE} = 3.581 \times \text{Vo}_2 + 1.448 \times \text{Vco}_2 - 32.4,$$

where EE is given in kcal/day, Vo_2 in L/day, and Vco_2 in L/day (10,12). All calculations are made at 1-min intervals, and the results are stored for further processing. The instrument allows for real-time graphics of Vo_2, Vco_2, and EE. Hard copies are obtained from an attached printer. The results of metabolic measurements were analyzed separately for the first 10 min [energy expenditure (EE1), oxygen consumption ($\text{Vo}_2$1)], and for the following 20 min (EE2, $\text{Vo}_2$2). The patients were considered to be in a steady state when Vo_2 and Vco_2 reached a stable plateau.

Table 3. Heart Rate, Systolic and Diastolic Blood Pressure, and Rate-Pressure Product in the Morning Before Premedication[a] and at the Time of VAS Evaluation[b]

Group	RPP1 (mm Hg·beats/min × 10^{-3})	RPP2 (mm Hg·beats/min × 10^{-3})	HR1 (beats/min)	HR2 (beats/min)	BPS1 (mm Hg)	BPS2 (mm Hg)	BPD1 (mm Hg)	BPD2 (mm Hg)
1	9.7 ± 2.5	10.0 ± 2.5	70 ± 10	73 ± 7	137 ± 22	136 ± 27	85 ± 13	79 ± 11
2	9.3 ± 1.9	8.6 ± 2.0[c]	72 ± 10[d]	65 ± 10[e]	128 ± 14	130 ± 13	81 ± 10	77 ± 8[f]
3	10.5 ± 3.2	11.4 ± 3.4[g]	76 ± 12	78 ± 12[h]	135 ± 21	145 ± 24	87 ± 15	89 ± 15[i]

$c < g$, $P = 0.019$; $d > e$, $P = 0.017$; $e < h$, $P = 0.006$; $f < i$, $P = 0.022$.

RPP, rate-pressure product; HR, heart rate; BPS, systolic blood pressure; BPD, diastolic blood pressure; VAS, visual analog scale.

[a] (HR1, BPS1, BPD1, and RPP1).

[b] (HR2, BPS2, BPD2, and RPP2).

Table 4. Results of Metabolic Measurements[a]

	EE1	EE2	BMR	Vo$_2$1	Vo$_2$2
Group 1 (atropine + meperidine)	2061 ± 365[b]	1787 ± 361[c]	1714 ± 267[d]	160 ± 29[e]	135 ± 17[f]
Group 2 (diazepam)	1807 ± 277[g]	1621 ± 269[h]	1774 ± 234[i]	137 ± 17[j]	124 ± 16[k]
Group 3 (placebo)	2079 ± 477[l]	1987 ± 394[m]	1760 ± 349[n]	153 ± 22[o]	144 ± 19[p]

Values are mean ± SD.

[a] Energy expenditure as calculated for the first 10 min (EE1, kcal/24 h) and for the following 20 min (EE2, kcal/24 h), predicted basal metabolic rate (BMR, kcal/24 h), oxygen consumption (mL·min^{-1}·m^{-2}) for the first 10 min (Vo$_2$1) and for the following 20 min (Vo$_2$2).

$b > d$, $P = 0.001$; $l > n$, $g > h$, $j > k$, $m > n$, $P = 0.0001$; $b > c$, $P = 0.004$; $i > h$, $P = 0.014$; $e > j$, $P = 0.034$; $e > f$, $P = 0.03$; $o > p$, $P = 0.045$; $p > k$, $P = 0.012$; $m > h$, $P = 0.021$.

Deltatrac was calibrated before every measurement according to the procedures suggested by the manufacturer of this device.

The measured EE values were compared with the patient's estimated basal metabolic rate (BMR). Basal metabolic rate is defined as the energy expenditure of a healthy subject at rest measured at least 10 h postprandially in a thermally neutral environment (10). The Deltatrac calculates BMR by means of the empirical Harris–Benedict formula:

$$\text{Males: BMR} = 66 + 13.8W + 5H - 6.8A,$$

$$\text{Females: BMR} = 655 + 9.6W + 1.8H - 4.7A,$$

where W = weight (kg), H = height (cm), A = age (yr), and BMR is given in kcal/24 h.

The data were analyzed using SYSTAT system (Evanston, Ill.). Analysis of variance was performed with post hoc comparisons by Tukey test. Paired and unpaired analyses were also performed on appropriately grouped data. For the VAS data, Kruskal–Wallis analysis of variance with Mann–Whitney U-test was performed and Bonferroni correction was made for the P values. A P value of 0.05 was considered significant.

Results

Demographic data (Table 1) in the three groups were similar with regard to age, weight, height, and sex distribution. Premedication in groups 1 and 2 was associated with greater degrees of subjective tiredness as measured by VAS than was placebo ($P = 0.001$ and $P = 0.003$, respectively) (Table 2). There was no significant difference in fear between the groups. The degree of subjective anxiolysis was greater in group 2 than in group 3 ($P = 0.007$). Dryness of mouth was most frequent and most severe in group 1 ($P = 0.0001$).

There were no differences in HR or blood pressure between the groups before premedication. At the time of VAS evaluation, patients in group 3 had statistically significantly higher levels of HR ($P = 0.006$), BPD ($P = 0.022$), and rate-pressure product (RPP) ($P = 0.019$) than did patients in group 2 (Table 3). Premedication caused a statistically significant decrease in HR in group 2 ($P = 0.017$). The rate-pressure product did not change significantly in any of the groups.

The calculated BMR values did not differ significantly in the three groups (Table 4). However, groups 1 and 3 had elevated measured energy expenditure levels (EE1) during the first 10 min when compared with their BMR values ($P = 0.001$ and $P = 0.0001$, respectively) as well as with EE1 values of group 2. In group 3, the energy expenditure (EE2) remained significantly above BMR for the following 20 min. In groups 1 and 2, energy expenditure decreased significantly during the 30-min measurement period ($P = 0.004$ and $P = 0.0001$, respectively); and in group

2 the EE2 decreased to levels significantly lower than BMR ($P = 0.001$). Oxygen consumption decreased significantly in all groups ($P = 0.015$ for group 1, $P = 0.0001$ for group 2, and $P = 0.045$ for group 3) during the 30-min measurement period. Oxygen consumption for the first 10 min was significantly higher in group 1 than in group 2 ($P = 0.034$). In group 3, the $V_{O_2}2$ was significantly greater than in group 2 ($P = 0.012$). The time needed to reach a steady state was significantly shorter in group 2 (7 ± 3 min) than in either group 1 (17 ± 3, $P = 0.0001$) or group 3 (17 ± 4, $P = 0.0001$).

Discussion

Premedication with intramuscular atropine plus meperidine or with oral diazepam produced a greater subjective sense of tiredness than did placebos with no significant difference in fear among patients given either of these two types of premedication and the placebos. The circulatory changes, however, indicated some anxiolytic effect in patients treated with diazepam. The subjective VAS estimates of patients given diazepam also gave an indication of better anxiolysis, although statistically significant when compared with placebo only. In earlier studies, the preoperative anxiolytic effect of different benzodiazepine derivatives has been demonstrated (3), although results showing poor anxiolytic effect have been published as well (14). In previous studies, we have found in both adults and children that benzodiazepines are as good as (15) or superior (16,17) to the combination of an opiate and anticholinergic agent. The present results indicate some superiority of an oral benzodiazepine derivative in comparison with intramuscular meperidine plus atropine (17).

The metabolic measurement was divided into two periods. When normal nonsedated subjects are first placed under the canopy, the V_{O_2} and V_{CO_2} are somewhat increased and then decrease over 5–15 min to a fairly stable plateau (10). As body O_2 stores are small compared with V_{O_2}, an increase in V_{O_2} represents an increase in tissue O_2 consumption. Thus, the V_{O_2} and V_{CO_2} values for the first 10 min reflect the anxiolytic and sedative effects of premedication as does the time needed to reach the plateau.

However, the possibly better anxiolytic effect of oral diazepam in comparison with intramuscular meperidine plus atropine may be of minor importance with respect to the metabolic response. The basal metabolic rate, after an overnight sleep, is remarkably constant for normal subjects of similar age, height, weight, and sex. Accordingly, the significantly elevated energy expenditure values indicate an iatrogenic stress factor. This can be either fear (indicating absence of anxiolysis) or a pharmacologic effect, or both. The V_{O_2} values in patients given atropine plus meperidine were surprisingly high (160 ± 29 $mL \cdot min^{-1} \cdot m^{-2}$) when compared with values in the diazepam-treated patients (137 ± 17 $mL \cdot min^{-1} \cdot m^{-2}$). The significance of this finding should be considered keeping in mind that there was no difference in anxiety, fear, tiredness, or in the hemodynamic variables.

Both atropine and meperidine have significant anticholinergic actions, and meperidine originally was studied as an atropinelike agent (18). Thus, the combination of atropine plus meperidine may change the balance between the sympathetic and parasympathetic nervous system more than the other generally used premedications (19–21), and therefore a sympathoadrenal reaction may be the best explanation for our findings of elevated metabolic activity.

It appears that the neuroendocrine stress induced by atropine plus meperidine is a rather high cost for the sedative and/or anxiolytic effect achieved. On the other hand, the observation that the measured energy expenditure in diazepam-treated patients decreased below predicted BMR values (for sex, weight, height, and age) could indicate a desirable effect of diazepam on the neuroendocrine system. Although myocardial oxygen consumption represents only 10%–15% of the total body oxygen consumption (22), it may be critical in patients with poor coronary reserve. Accordingly, use of premedications causing increased BMR rates and thus increased V_{O_2} values should be reconsidered in cardiac-compromised patients.

In conclusion, our results show that even premedication can cause a significant effect on the metabolic response of healthy patients before operation. Premedication with atropine plus meperidine induces a marked metabolic response characterized by increased overall metabolic rate and, in particular, by increased oxygen consumption. Diazepam premedication attenuates the metabolic response to preoperative stress and even lowers the overall metabolic rate below predicted values. Further studies evaluating the metabolic response to premedication in sick patients who are at risk for acute episodes of hypoxia are urgently needed.

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Blood Pressure Measurement by Arterial Tonometry in Controlled Hypotension

Osamu Kemmotsu, MD, PhD, FCCM, Mitsuo Ueda, MD, Hiroshi Otsuka, MD, Takeyasu Yamamura, MD, PhD, Atsushi Okamura, MD, Takehiko Ishikawa, MD, Dean C. Winter, PhD, and Joseph S. Eckerle, SM

Department of Anesthesiology, Hokkaido University School of Medicine, Sapporo, Japan; Department of Biosciences and Bioengineering, Southwest Research Institute, San Antonio, Texas; Medical Research Laboratory, Stanford Research Institute International, Menlo Park, California

A newly developed arterial tonometer enabled us to measure the blood pressure waveforms in addition to determining systolic and diastolic pressures noninvasively and continuously. Twenty-eight adult patients undergoing orthopedic surgery under controlled hypotension were studied. Systolic blood pressure was reduced to two-thirds of baseline values with an infusion of nitroglycerin during nitrous oxide/enflurane anesthesia. Intraarterial blood pressures were simultaneously measured in either the right or the left radial artery with a cannula and a Gould P23XL calibrated transducer; tonometric monitoring was performed on the contralateral radial artery using a Colin CBM-3000 instrument. The outputs of the two blood pressure measurement instruments were recorded for later data analysis. The shape of the tonometric pressure waveform was nearly identical to the waveform recorded intraarterially even during controlled hypotension. Regression analyses of 2039 paired tonometric and intraarterial blood pressure values during the hypotensive period showed good correlations (r = 0.78 for systolic, r = 0.81 for mean, and r = 0.70 for diastolic pressures). The accuracy of systolic, mean, and diastolic readings was from 4 to 7 mm Hg with negligible bias and did not differ significantly among six systolic, four mean, and four diastolic pressure groups. Our results indicate that arterial tonometry can provide accurate, reliable, and real-time monitoring of blood pressure even during controlled hypotension.

(Anesth Analg 1991;73:54–8)

A newly developed system for arterial tonometry enabled us to measure the entire blood pressure waveform and to determine the systolic, mean, and diastolic blood pressures noninvasively and continuously (1,2). As we reported previously (2), the tonometric blood pressure (TBP) waveform is identical to that of intraarterial blood pressure (IBP). Regression analyses of the paired values for TBP and IBP during anesthesia showed good correlations for a wide range of ages and for either sex.

We routinely monitor the blood pressure waveform in controlled hypotension where arterial blood pressure is intentionally reduced with rapid-acting vasodilator agents such as nitroglycerin. Therefore, intraarterial cannulation is usually performed to obtain beat-to-beat blood pressure (3,4). However, because of its invasive nature complications such as infections, thromboemboli, and trauma may accompany intraarterial cannulation (4,5).

If satisfactory results can be obtained using noninvasive TBP monitoring during controlled hypotension, the reliability of the technique in this clinical situation will have been demonstrated. The aim of the present study was to evaluate the accuracy, reliability, and clinical acceptability of TBP measurement by comparing it with invasive measurements of blood pressure during controlled hypotension.

Methods

The study population consisted of 28 adult patients (15 women, 13 men; average age, 32 yr) scheduled for elective surgery under controlled hypotension. Approval from the Hokkaido University Hospital Ethics Committee was granted for the study, and written informed consent was obtained from each patient.

In each patient, oscillometric blood pressure deter-

Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Accepted for publication February 20, 1991.

Address correspondence to Dr. Kemmotsu, Department of Anesthesiology, Hokkaido University School of Medicine, N-15, W-7, Kita-ku Sapporo, Japan 060.

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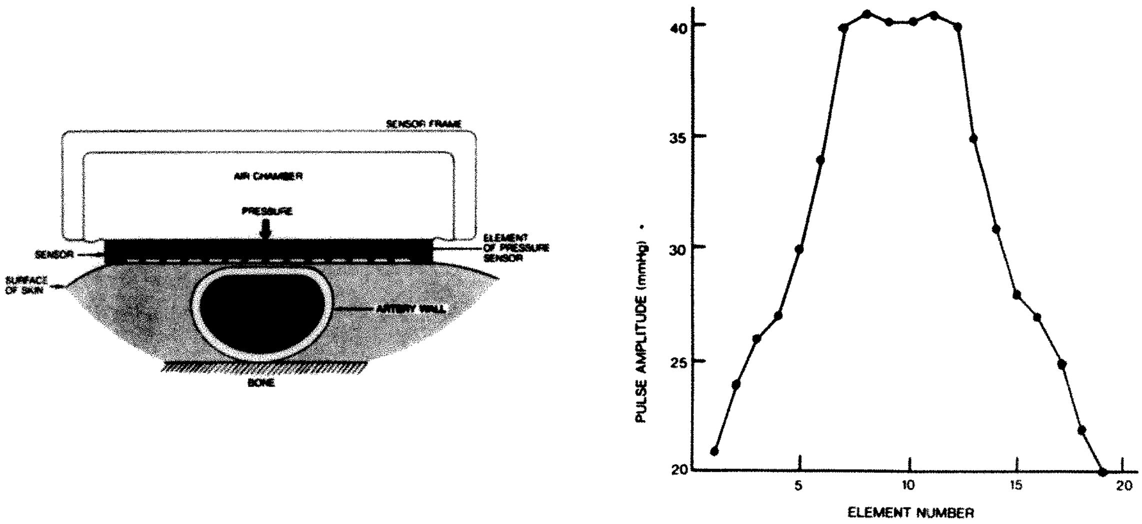

Figure 1. *Left:* a schematic drawing showing how the tonometer sensor flattens the artery against the bone. Transducer elements over the flattened portion of the artery are used to measure blood pressure. *Right:* a typical graph for the pulse-pressure amplitude on each of the transducer elements in the tonometer used for blood pressure measurements.

minations were performed bilaterally before induction of anesthesia to exclude patients with blood pressure differences between arms. A Teflon 22-gauge intraarterial cannula was inserted under local anesthesia into either the right or left radial artery depending on Allen's tests. The cannula was connected to a Gould P23XL calibrated transducer to measure IBP. A resonance overshoot eliminator device (Spectramed, Oxnard, Calif.; refers to this device by the acronym ROSE) was placed in the arterial monitoring system when needed. Tonometric blood pressure was monitored using a Colin CBM-3000 tonometric instrument (Colin Electronics, Komaki, Japan) on the contralateral radial artery.

The arterial tonometer uses a sensor placed on the wrist over the radial artery. The sensor exerts sufficient pressure on the skin to flatten partially the underlying radial artery. When the artery is flattened in this way, the IBP is transmitted through the skin with nearly perfect fidelity. This phenomenon is explained by the fact that tension forces on the artery wall are perpendicular to the forces exerted by the sensor and by the blood pressure acting on the inner surface of the artery wall (6). As a practical matter, it is very difficult to position properly a basic tonometer consisting of only a single pressure transducer relative to the underlying artery. The array of 15 piezoresistive pressure transducers in the Colin arterial tonometer sensor makes positioning of the sensor relatively easy. A schematic representation of the multiple transducer sensor and the underlying radial artery is shown in Figure 1. Normally, at least one of 15 transducers will be properly positioned relative to the artery. A computer analyzes the signals from the tonometer sensor, selects the transducer from the array that is properly positioned, and sends the signal from the selected transducer to the cathode ray tube display.

Both the TBP and IBP signals as well as the electrocardiogram were continuously monitored and recorded on a PCM magnetic tape recorder and by a computer. Data-acquisition software recorded pressure measurements every 30 s for later data analysis. Anesthesia was induced by thiamylal (5 mg/kg IV), and the trachea was intubated using vecuronium (0.1 mg/kg IV). Respiration was controlled to maintain normocapnia as determined by capnography (Ohmeda model 2100). Anesthesia was maintained with enflurane (1%–2%) in nitrous oxide 4 L/min and oxygen 2 L/min. Systolic blood pressure was reduced to two-thirds of the preanesthetic baseline levels by an infusion of nitroglycerin (0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Regression analyses of the pressure data were done separately for the prehypotensive, hypotensive, and recovery periods. Mean values for differences between TBP and IBP and confidence intervals were also calculated. Precision (mean absolute value of error) and bias (mean error) were also calculated for systolic, mean, and diastolic TBP values with IBP used as the reference value (7,8). Changes in precision and bias as a function of pressure were calculated by dividing the systolic data points into six groups (≤79, 80–99, 100–119, 120–139, 140–159, and ≥160 mm Hg), the mean data points into four groups (≤59, 60–79, 80–99, and ≥100), and the diastolic data points into four groups (≤39, 40–59, 60–79, and ≥80 mm Hg). Student's *t*-test was used to compare each group with the group having the best

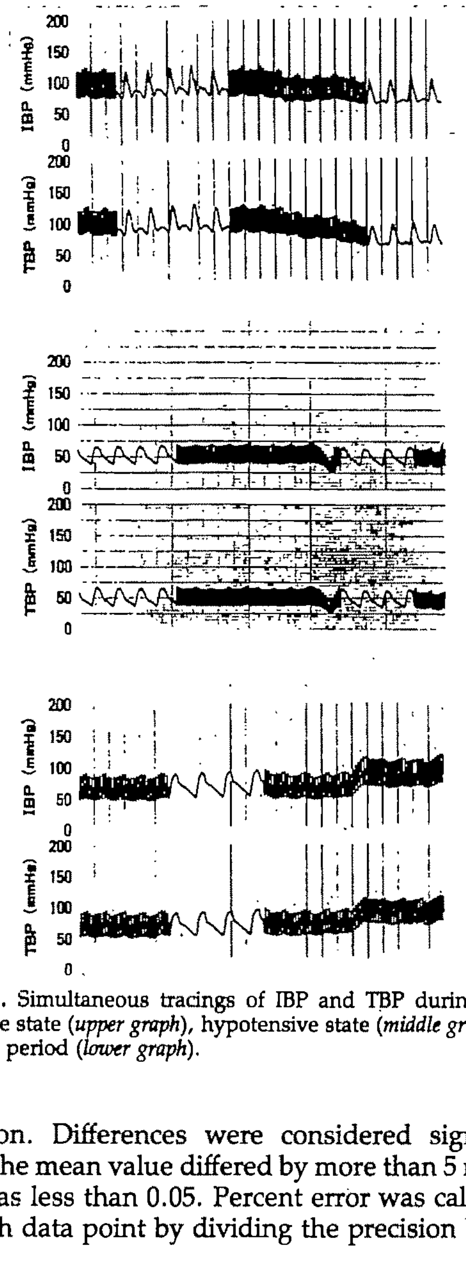

Figure 2. Simultaneous tracings of IBP and TBP during prehypotensive state (*upper graph*), hypotensive state (*middle graph*), and recovery period (*lower graph*).

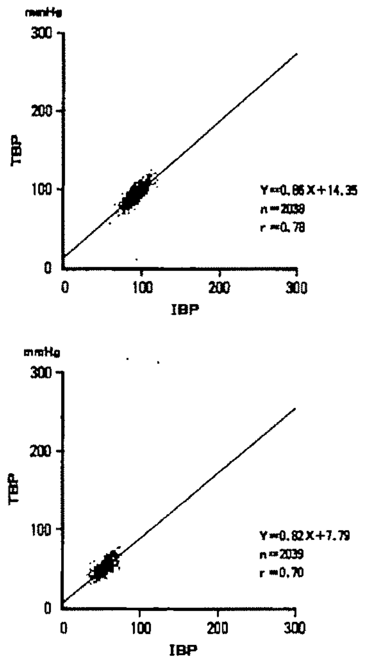

Figure 3. Scatterplots between IBP and TBP for systolic (*upper graph*) and diastolic blood pressures (*lower graph*) based on 2039 paired points obtained during hypotensive periods in 28 patients.

precision. Differences were considered significant when the mean value differed by more than 5 mm Hg or P was less than 0.05. Percent error was calculated for each data point by dividing the precision by IBP.

Results

Waveforms for IBP and TBP in a 32-yr-old, 58-kg man during induction of controlled hypotension, the hypotensive period, and the recovery period are shown in Figure 2. These IBP and TBP waveforms appear nearly identical.

Regression analyses for 2039 paired TBP and IBP measurements from 28 patients during the hypotensive period show good correlations for systolic (r = 0.78, $P < 0.001$), mean (r = 0.81, $P < 0.001$), and diastolic pressures (r = 0.70, $P < 0.001$). These data are shown in Figure 3. Regression analyses of the data during the prehypotensive and recovery periods are summarized in Table 1. Mean differences between TBP and IBP together with confidence intervals for these means are also shown in Table 1.

A high correlation existed between increases and decreases in IBP values (ΔIBP) and corresponding changes in TBP (ΔTBP) for systolic pressures (r = 0.78, $P < 0.001$) as shown in Figure 4. There were also significant correlations between IBP and TBP changes for mean (r = 0.76, $P < 0.001$) and diastolic pressures (r = 0.68, $P < 0.001$).

Pooled precision and bias data are summarized in Table 2. Systolic, mean, and diastolic precision values did not differ significantly among the six systolic pressure groups, the four mean pressure groups, and the four diastolic pressure groups. Precision, as defined by Sheiner and Beal (7), was typically 4–7 mm Hg, and there is a negligible bias in the measurements. Percent error was larger in diastolic pressure groups than in mean and systolic pressure groups, but the mean error was always less than 10%.

Discussion

Blood pressure must be monitored continuously in the anesthesia management of patients during controlled hypotension when blood pressure is artificially reduced with an infusion of vasodilator drugs such as nitroglycerin. Thus, IBP monitoring is often

Table 1. Regression Analysis Data

	Prehypotensive (n = 1888)			Hypotensive (n = 2039)			Recovery (n = 451)		
	Systolic	Mean	Diastolic	Systolic	Mean	Diastolic	Systolic	Mean	Diastolic
r	0.91	0.90	0.83	0.78	0.81	0.70	0.93	0.89	0.85
RE	0.84 × 12.64	0.89 × 8.2	0.94 × 0.82	0.86 × 14.35	1.03 × −2.4	0.82 × 7.79	0.97 × 0.99	1.01 × −3.5	1.04 × −5.14
Standard deviation	0.5	1.2	−2.2	1.4	1.3	−2.1	−2.2	−1.5	−2.1
	6.4	5.4	5.9	5.9	5.6	5.8	6.7	5.8	6.3
Confidence interval for mean									
95%	±0.29	±0.30	±0.38	±0.31	±0.30	±0.40	±0.62	±0.66	±0.81
99%	±0.27	±0.26	±0.35	±0.30	±0.28	±0.40	±0.58	±0.61	±0.77

n, Number of measurements; r, regression coefficient; RE, regression equation.

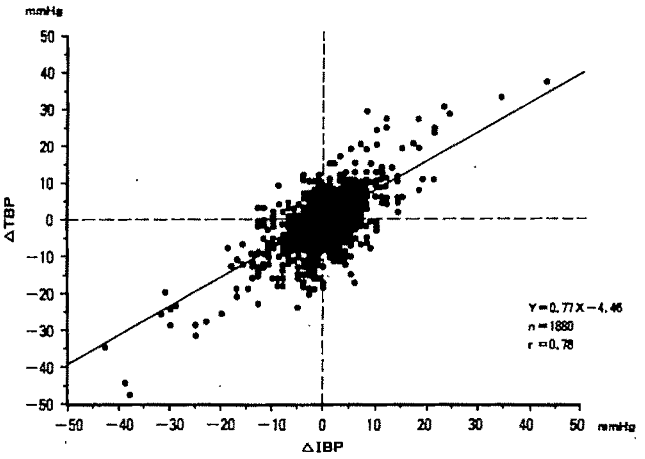

Figure 4. Relation between ΔIBP and ΔTBP for systolic blood pressure based on 1880 paired points.

Table 2. Pooled Precision and Bias of Tonometric Blood Pressure for Various Blood Pressure Ranges

Range (mm Hg)	Precision	Bias	Percent error
Systolic			
All	5.4 ± 3.7	−0.66 ± 6.6	5.5 ± 3.9
≤79	6.1 ± 3.7	−5.6 ± 4.5	8.1 ± 5.0
80–99	5.3 ± 3.6	−1.5 ± 6.2	5.8 ± 3.9
100–119	5.3 ± 4.2	0.39 ± 6.7	4.9 ± 3.8
120–139	6.9 ± 3.5	3.4 ± 7.0	5.4 ± 2.8
140–159	5.7 ± 3.1	3.6 ± 5.5	3.9 ± 2.1
≥160	5.4 ± 2.2	4.4 ± 4.0	3.3 ± 1.4
Mean			
All	4.1 ± 2.9	0.65 ± 5.0	5.9 ± 4.3
≤59	3.6 ± 2.3	1.8 ± 3.9	6.3 ± 4.1
60–79	4.3 ± 3.1	0.50 ± 5.2	6.2 ± 4.5
80–99	4.0 ± 3.0	0.43 ± 4.9	4.6 ± 3.4
≥100	4.5 ± 2.8	−0.35 ± 5.3	4.2 ± 2.6
Diastolic			
All	5.6 ± 3.2	2.7 ± 5.8	9.8 ± 5.6
≤39	3.5 ± 2.0	−0.80 ± 4.0	9.4 ± 5.4
40–59	5.2 ± 3.1	3.0 ± 3.0	9.9 ± 5.9
60–79	6.5 ± 3.2	2.3 ± 6.8	9.9 ± 4.9
≥80	5.8 ± 3.6	2.1 ± 6.5	6.8 ± 4.3

Values are expressed as mean ± SD.

considered to be essential in controlled hypotension (4). However, because of the invasive nature of IBP monitoring, complications such as vascular compromise, disconnection, accidental injection, infection, and damage to nearby nerves may be associated with such arterial cannulation (5).

Our data indicate that TBP measurement during controlled hypotension can provide safe, accurate, reliable, and real-time blood pressure information together with pressure waveforms that correlate favorably with IBP measurement. Differences between IBP and TBP values were small over a wide range of systolic, mean, and diastolic blood pressure values. This was proved by the good correlations between IBP and TBP and by the similar magnitudes of the precision values for different pressure groups.

As we reported previously (2), overshoot (which often occurs in the IBP waveform) does not occur in the TBP waveform. This is an added advantage of the tonometry system. Thus, tonometry apparently provides blood pressure values and waveforms that are as reliable as conventional IBP measurement in clinical anesthesia where vasodilator agents are used. This is also true in several anesthesia cases of 11-h duration, which were not included in the present data. Therefore, we conclude that arterial tonometry can reduce the need for conventional, invasive IBP monitoring methods during controlled hypotension as well as during the normotensive state. This is especially true if the tonometer is used with pulse oximetry and capnography, which can reduce the need for repeated measurements of arterial blood gas tensions during anesthesia. Also, the use of these noninvasive modalities avoids hazards related to intraarterial cannulation. Safety considerations related to AIDS and hepatitis, which are becoming a serious problem among operating room personnel, also favor use of noninvasive methods.

This research was supported by Colin Electronics Company, Ltd., Komaki, Japan. The clinical test was carried out at Hokkaido University Hospital using tonometers built by Colin Electronics.

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Mixtures of Sodium Nitroprusside and Trimethaphan for Induction of Hypotension

Kenji Nakazawa, MD, Chikuni Taneyama, MD, Kirk T. Benson, MD,
Gregory K. Unruh, MD, and Hiroshi Goto, MD

Department of Anesthesiology, University of Kansas Medical Center, Kansas City, Kansas

A mixture of sodium nitroprusside (SNP) and trimethaphan, empirical 1:10 weight ratio, has been advocated to decrease untoward side effects of SNP when used to induce hypotension during anesthesia and operation. The purpose of this study was to investigate the effects of various ratios of mixtures of SNP and trimethaphan on heart rate (HR), renal sympathetic nerve activity (RSNA), and renal artery blood flow to find the best ratio of SNP and trimethaphan for producing induced hypotension. Five mixtures with different ratios of SNP and trimethaphan, as well as each drug alone, were given intravenously to mongrel dogs in amounts adequate to achieve a stable mean arterial blood pressure of 75 ± 5 mm Hg. Sodium nitroprusside alone significantly increased HR (163% ± 14.5%) and RSNA (222% ± 24%). Trimethaphan alone significantly decreased RSNA (11.6% ± 4.5%). There were significant positive correlations between SNP-to-trimethaphan ratios and percent changes in HR ($r^2 = 0.301$, $P < 0.01$) and in RSNA ($r^2 = 0.648$, $P < 0.01$). Renal artery blood flow was well maintained with all ratios. Sodium nitroprusside and trimethaphan interacted synergistically to produce hypotension. However, they antagonize each other in their effects on arterial baroreflex-mediated changes in HR and RSNA. According to linear regression lines, HR changed least with a SNP-to-trimethaphan ratio of 1:5, and RSNA changed least with SNP-to-trimethaphan ratios of 1:2.5 and 1:5. Our results indicate that mixtures of SNP and trimethaphan in ratios of approximately 1:2.5 to 1:5 may produce induced hypotension with stable reflex sympathetic nerve activity.

(Anesth Analg 1991;73:59–63)

Sodium nitroprusside (SNP) is a potent vasodilator with a short duration of action that provides both a rapid onset of hypotension and a rapid return of arterial blood pressure. Sodium nitroprusside is not, however, without untoward side effects. MacRae et al. (1) reported that a total dose of SNP could be considerably reduced by adding trimethaphan. They chose a SNP-to-trimethaphan weight ratio of 1:10 because the proportion of 1:10 would seem to approximate the relative potencies of the two drugs when used separately. It is well known that SNP is associated with increased arterial baroreflex activities resulting in tachycardia and in increased renal sympathetic nerve activity (RSNA). On the other hand, trimethaphan decreases efferent sympathetic nerve activity because of its ganglionic blocking property. Renal artery blood flow (RBF) may be reduced by trimethaphan (2). The purpose of this study was to investigate the effects of various ratios of an SNP and trimethaphan mixture on heart rate (HR), RSNA, and RBF to find the best mixture of SNP and trimethaphan for induced hypotension.

Methods

This study was approved by the Kansas University Institutional Animal Care and Use Committee, and appropriate guidelines for the use of animals were observed during all aspects of this study.

Seven adult mongrel dogs of either sex, weighing between 12.0 and 24.0 kg, were starved overnight but had free access to water. Anesthesia was induced with thiopental (10 mg/kg IV) and α-chloralose (100 mg/kg IV) and was maintained with α-chloralose (bolus dose 40 mg/kg every 2 h). The dogs were paralyzed with pancuronium (0.1 mg/kg IV) to avoid inaccuracies on the measurements of RSNA secondary to muscular movement. Intubation of the trachea followed immediately after the induction of anesthesia, and the lungs were mechanically ventilated with a Harvard animal ventilator (Millis, Mass.) with 100% oxygen at a tidal volume of 10–15 mL/kg and a

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Presented in part at the 1990 Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada.

Accepted for publication February 27, 1991.

Address correspondence to Dr. Goto, Department of Anesthesiology, University of Kansas Medical Center, 39th and Rainbow Boulevard, Kansas City, KS 66103.

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0003-2999/91/$3.50

frequency of 15–20 cycles/min to maintain $Paco_2$ between 35 and 40 mm Hg. Adequate fluid balance was ensured by an infusion of 5% dextrose in 0.9% saline solution, 4 $mL{\cdot}kg^{-1}{\cdot}h^{-1}$; and normothermia was maintained by using a heating blanket.

Arterial pressure and central venous pressure were measured directly from the femoral artery and the external jugular vein with pressure transducers (DXT Spectramed, Oxnard, Calif.). Mean arterial pressure (MAP) was derived by electronic integration of the pulsatile pressure signal. Heart rate was calculated from lead II of the electrocardiogram using a cardiotachometer (1321, San-ei, Japan).

The left kidney was exposed retroperitoneally by a left flank incision. An ultrasonic transit time blood flowmeter (T201COS, Transonic System, Ithaca, N.Y.) was placed around the renal artery. Renal sympathetic nerves along the renal artery were isolated using a microscope, and the distal end of the strands were crushed, immersed in mineral oil, and placed on a bipolar silver electrode for recording the renal nerve discharges. Electrical impulses recorded from the renal sympathetic nerves were amplified using a preamplifier (AVB 10 [bandwidth: 50–1000 Hz], Nihon Kohden, Japan). The amplified nerve discharges were visualized on a dual-beam oscilloscope (VC 11, Nihon Kohden) and monitored by an audiospeaker. The neurogram was integrated by a resistance-capacitance integrator circuit (time constant, 2.0 s). As integrated output is dependent on the voltages and frequencies of RSNA, it was used as a measurement of overall RSNA. The resting spontaneous nerve activity was normalized to 100% in each nerve preparation for comparison. Nerve activity was recorded in all dogs after death as a measurement of the level of zero "noise."

Solutions of SNP, trimethaphan, and their mixtures were prepared in 5% dextrose solution in 50-mL foil-wrapped syringes and were infused from a Harvard pump. Seven different ratios of SNP to trimethaphan (0:1, 1:10, 1:5, 1:2.5, 1:1, 1:0.5, 1:0) were prepared.

At least 30 min were allowed after surgical preparation to establish a stable hemodynamic state before infusion of hypotensive agents. Sodium nitroprusside alone, trimethaphan alone, and each one of the five mixtures were alternately infused in a random fashion to produce equihypotensive conditions. Arterial blood pressure was gradually decreased to 75 ± 5 mm Hg over 10 min and was maintained for the next 10 min by titrating the infusion rate of SNP, trimethaphan, or their mixtures. The latter 10 min was designated as "stable" 10 min. At least 1 h elapsed between each infusion to ensure that all variables returned to baseline values.

Cardiovascular values and nerve activities were continuously measured and recorded by means of a DAT tape PCM recorder (RD-100T, TEAC, Montebello, Calif.), which was played back on a multichannel chart recorder (Omnicorder 8M14, San-ei). The infusion rate ($\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$) was averaged over the 10 min of stable MAP at 75 ± 5 mm Hg. Variables recorded at the end of the stable 10 min were used for data analysis.

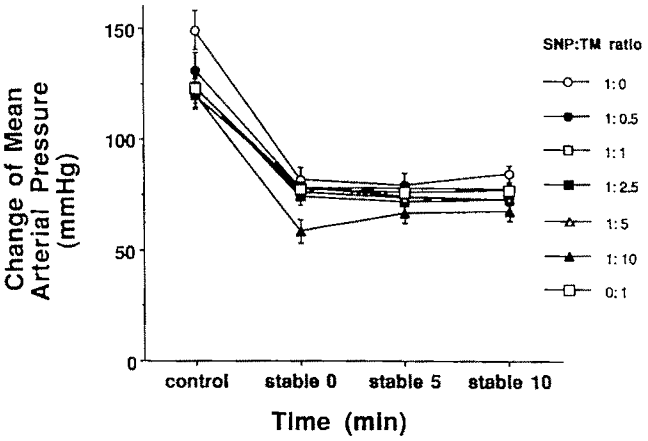

Figure 1. Changes in MAP during induced hypotension by various ratios of SNP, trimethaphan, and their mixtures. Note that MAP was stable at 75 ± 5 mm Hg with each infusion during stable 10 min.

All data were expressed as mean ± SEM. Comparisons within experimental protocols were made using a repeated measurement analysis of variance. Multiple comparisons between individual means were performed using the Newman–Keuls method. Differences with a statistical probability of less than 0.01 were considered significant.

Results

Baseline levels of MAP, HR, and central venous pressure were 127 ± 3 mm Hg, 131 ± 6 beats/min, and 3 ± 2 mm Hg, respectively. A reduction in MAP to 75 ± 5 mm Hg was achieved in 10 min by SNP, trimethaphan, or their mixtures (Figure 1). Thereafter, MAP was maintained at 75 ± 5 mm Hg for the next 10 min (stable 10 min) by titrating the infusion rate. No significant differences in MAP were found among all ratios of SNP and trimethaphan 10 min after stable hypotension was established.

Figure 2 shows changes in MAP, HR, and RSNA after intravenous injections of various mixtures of SNP and trimethaphan. Sodium nitroprusside alone produced significant increases in both HR and RSNA, and trimethaphan alone produced a significant decrease in RSNA at the same MAP of 75 ± 5 mm Hg. A mixture with a 1:2.5 ratio of SNP and trimethaphan produced a minimal change in RSNA at a MAP of 75 ± 5 mm Hg.

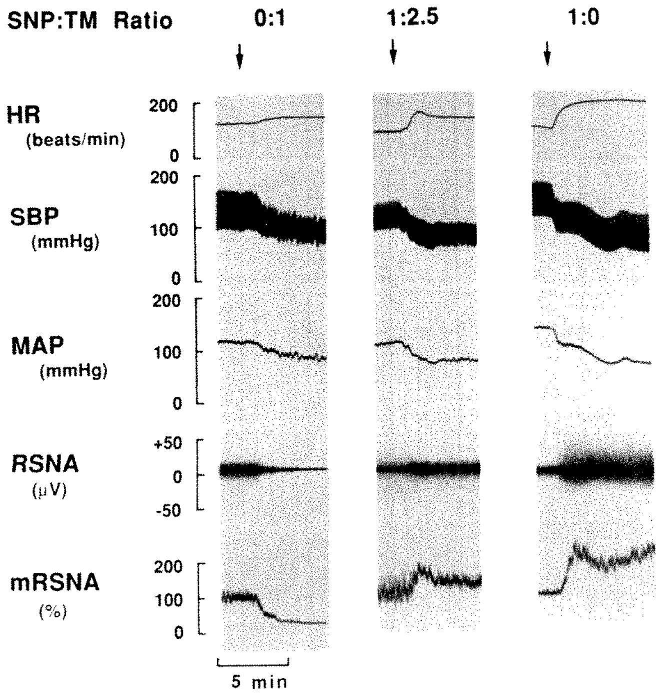

Figure 2. One of the examples of MAP, HR, and RSNA after intravenous injections of trimethaphan alone (SNP-to-trimethaphan ratio, 0:1), SNP alone (SNP-to-trimethaphan ratio, 1:0), and an SNP-to-trimethaphan ratio of 1:2.5.

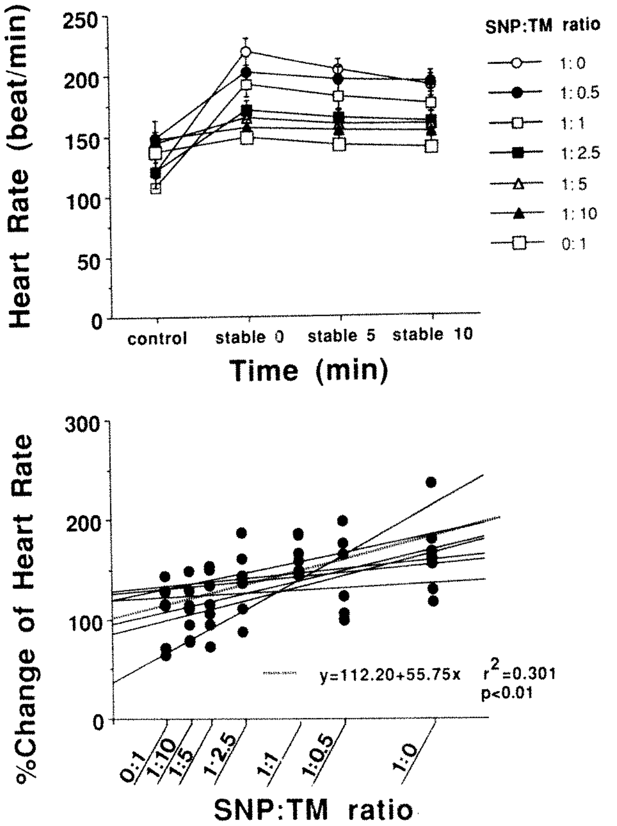

Figure 3. Changes in HR during induced hypotension by various ratios of SNP and trimethaphan mixtures (*top*). Correlation between SNP-to-trimethaphan ratio and percent changes in HR at 10 min after stable induced hypotension (*bottom*). *Solid lines*, regression lines constructed from individual animals; *dashed line*, mean regression line.

Heart rate at the end of the stable 10 min was significantly increased above baseline levels with 1:0, 1:0.5, 1:1, and 1:2.5 ratios of SNP and trimethaphan (Figure 3, top).

Percent changes in HR from control values in each dog were plotted with respect to the ratio of SNP to trimethaphan. There was a significant positive correlation between the ratio of SNP to trimethaphan and percent changes in HR ($r^2 = 0.301$, $P < 0.01$) (Figure 3, bottom).

Figure 4 (top) shows the time-course of changes of RSNA. Renal sympathetic nerve activity increased to 222% ± 24% with an SNP-to-trimethaphan ratio of 1:0 (SNP alone) and decreased to 11.6% ± 4.5% with trimethaphan alone.

In each dog, the percent changes in RSNA from baseline values were plotted against the SNP-to-trimethaphan ratio (Figure 4, bottom). There was a significant positive correlation between SNP-to-trimethaphan ratio and percent change of RSNA ($r^2 = 0.648$, $P < 0.01$).

Renal blood flow was well maintained (Figure 5, top). However, it increased significantly with SNP alone (150.3% ± 25%). Calculated renal arterial resistance decreased significantly with all ratios of SNP and trimethaphan (Figure 5, bottom).

Table 1 shows average infusion rates of SNP alone, trimethaphan alone, and their mixtures during 10 min of stable MAP at 75 ± 5 mm Hg. A modified isobologram (3) was constructed to determine whether the mixtures of SNP and trimethaphan interact additively or synergistically. The average infusion rate of SNP alone was placed on the ordinate, and the average infusion rate of trimethaphan alone was placed on the abscissa in the modified isobologram. All points for the mixtures were found to be below the additive line (Figure 6).

Discussion

In our experiments, induced hypotension to 75 ± 5 mm Hg was gradually accomplished by various ratios of SNP and trimethaphan over 10 min (Figure 1) because abrupt reduction of MAP might increase arterial baroreflex activity. Sodium nitroprusside and trimethaphan are compatible in 5% dextrose solution without forming precipitates. They were mixed just before use to avoid possible chemical changes with time. α-Chloralose was used for maintenance of anesthesia because it does not depress arterial barore-

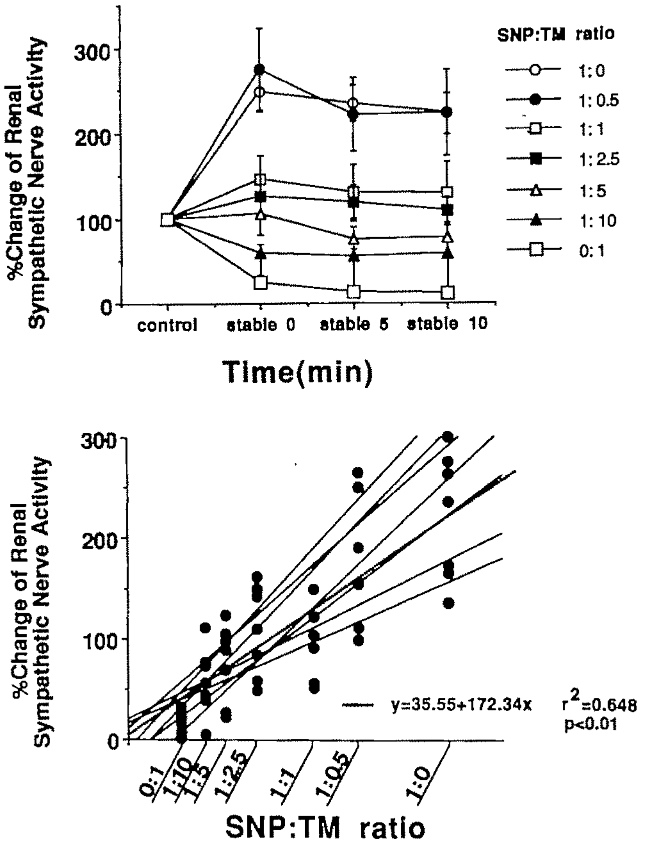

Figure 4. Changes in RSNA during hypotension induced by SNP and trimethaphan mixtures of various ratios (*top*). Correlation between SNP-to-trimethaphan ratio and percent changes of RSNA at 10 min after stable induced hypotension (*bottom*). *Solid lines*, regression lines constructed from individual animals; *dashed line*, mean regression line.

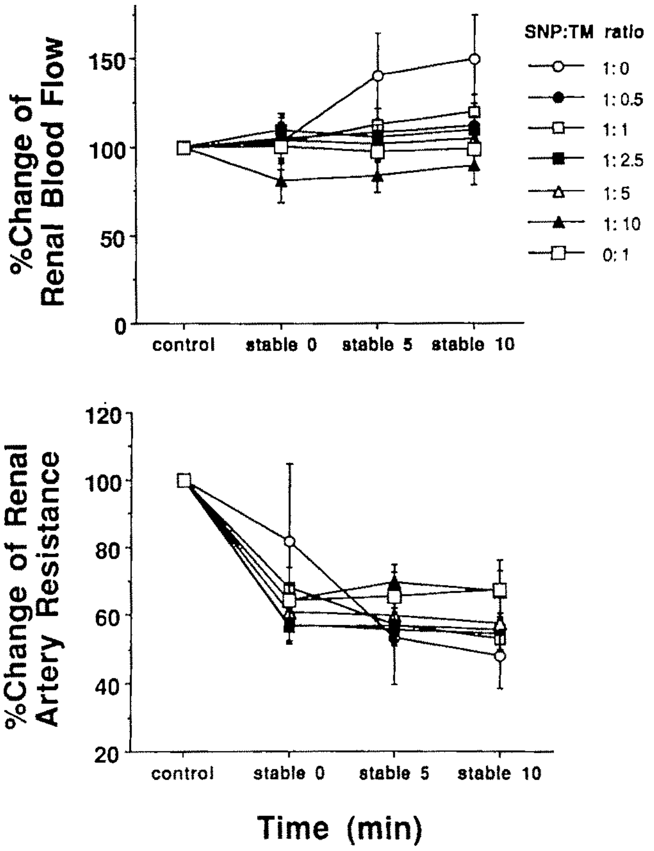

Figure 5. Percent changes in RBF during hypotension induced by SNP and trimethaphan mixtures of various ratios and times after stable state (*top*). Calculated renal arterial resistance was decreased with each infusion during induced hypotension (*bottom*).

flex (4–6). Thiopental, known to attenuate arterial baroreflex (7), was used only for the induction of anesthesia and the actual experiment was begun at least 2 h after thiopental injection.

Sodium nitroprusside has been found not to attenuate arterial baroreflex (8). Therefore, significant increases in HR and RSNA were observed when SNP was used alone (Figures 2–4). On the other hand, trimethaphan alone decreased RSNA significantly in all dogs because of its ganglionic blocking property (Figures 2 and 4). However, HR increased in some of our dogs with trimethaphan alone (Figure 3) because trimethaphan may increase or decrease HR, depending on the balance between the sympathetic and parasympathetic systems before the infusion of trimethaphan (9,10).

The significant correlations (smaller increases in HR or RSNA with decreasing ratio of SNP to trimethaphan [Figures 3 and 4]) are thought to be due to two mechanisms: (a) lower SNP infusion ratios, which elicit less degree of arterial baroreflex, and (b) higher trimethaphan infusion rates, which block the arterial baroreflex pathway to a greater extent at sympathetic ganglia.

Therefore, SNP and trimethaphan are antagonistic to each other with respect to baroreflex control of HR and sympathetic nerve activities. At the same time, lower SNP doses in the mixtures will minimize non-baroreflex-mediated untoward effects such as a production of cyanide. Similarly, undesirable side effects of trimethaphan such as histamine release and prolonged hypotension after discontinuation of trimethaphan can be minimized with the mixtures. It has been shown that trimethaphan may decrease RBF; however, in our study, RBF remained unchanged, even with trimethaphan alone, owing to the reduction of renal arterial resistance (Figure 5).

The doses of both hypotensive agents in all ratios of mixtures were indeed much less than the dose of either trimethaphan or SNP given alone (Table 1). This indicates that both hypotensive agents work either additively or synergistically. To clarify this, data from our study and the clinical study by MacRae et al. (1) were fed into the modified isobologram (Figure 6). Points for all ratios of SNP and trimethaphan were found to be

Table 1. Average Infusion Rates of Sodium Nitroprusside Alone, Trimethaphan Alone, and Their Mixtures During 10 Minutes of Stable Mean Arterial Pressure at 75 ± 5 mm Hg

	SNP:TM ratio						
	0:1	1:10	1:5	1:2.5	1:1	1:0.5	1:0
Infusion rates							
SNP ($\mu g \cdot kg^{-1} \cdot min^{-1}$)		1.2 ± 0.2	1.3 ± 0.2	2.7 ± 1.1	4.6 ± 1.4	5.7 ± 1.8	9.6 ± 0.9
TM ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	140 ± 30.9	12.4 ± 2.0	6.5 ± 0.8	6.8 ± 0.3	4.6 ± 1.4	2.9 ± 0.9	

SNP, sodium nitroprusside; TM, trimethaphan.

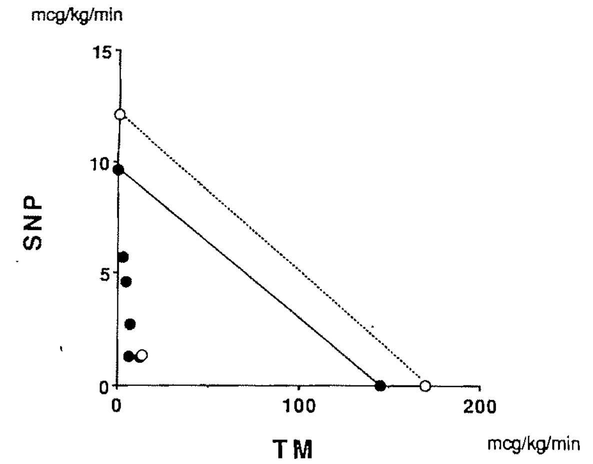

Figure 6. Modified isobologram for the interaction of SNP and trimethaphan in producing induced hypotension at 75 ± 5 mm Hg. *Point ●, solid additive line,* from our data. *Point ○, dashed additive line,* from data of MacRae et al. (1).

below the additive line. This means that SNP and trimethaphan interact synergistically to produce hypotension. Although lower hypotensions were achieved in MacRae's study, SNP or trimethaphan dosage was similar when either was used alone (Figure 6). This may indicate that dogs and humans respond to SNP and trimethaphan similarly. The reason why trimethaphan and SNP interact synergistically to produce hypotension is not clear, but the synergism may be related to the fact that they produce hypotension by two different mechanisms—by direct action on vascular beds (SNP), and by blocking sympathetic ganglia (trimethaphan).

Tachycardia during SNP-induced hypotension may be detrimental for patients with ischemic heart disease. Increased sympathetic nerve activity leads to release of endogenous catecholamines and may activate the renin-angiotensin system (11). Depressed sympathetic nerve activity produced by trimethaphan, on the other hand, may be dangerous when acute blood loss occurs as compensatory arterial baroreflex is limited (12). For these reasons, it is conceivable that stable HR and sympathetic nerve activity are important during induced hypotension. Heart rate remained relatively unchanged with ratios of 0:1, 1:10, 1:5, and 1:2.5 for SNP and trimethaphan mixtures, and RSNA remained unchanged with 1:5, 1:2.5, and 1:1 ratios. Therefore, ratios of 1:5 and 1:2.5 for SNP and trimethaphan gave the best mixtures in our experimental preparation.

In conclusion, SNP and trimethaphan interact synergistically to induce arterial hypotension. By mixing the two agents, untoward side effects of both can be minimized as their effects on baroreflex-mediated responses to induced hypotension are antagonistic and as absolute doses of both agents can be decreased significantly. The 1:2.5 and 1:5 ratios of SNP and trimethaphan may be the best to produce stable arterial baroreflex during induced hypotension.

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Effects of Isoflurane, Midazolam, and Etomidate on Cardiovascular Responses to Stimulation of Central Nervous System Pressor Sites in Chronically Instrumented Cats

Karl A. Poterack, MD, John P. Kampine, MD, PhD, and William T. Schmeling, MD, PhD

Departments of Anesthesiology and Pharmacology, The Medical College of Wisconsin and Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin

The systemic hemodynamic actions of isoflurane (a volatile anesthetic) and etomidate and midazolam (intravenous anesthetics) have been well documented. However, few studies have investigated the actions of these agents on central cardiovascular control sites. The present investigation examined the actions of these agents on the responses of systolic arterial pressure (SAP), heart rate, infrarenal aortic blood flow, and lower body vascular resistance to central nervous system pressor site stimulation in chronically instrumented cats. Male and female cats ($n = 23$) were chronically instrumented with bipolar stimulating electrodes in the regions of the ventrolateral hypothalamus (anterior, 10.0 mm; lateral, 2.5 mm; depth, −4.0 mm) and mesencephalic reticular formation (anterior, 2.0 mm; lateral, 2.0 mm; depth, −1.0 mm). Control experiments consisted of stimulation sequences at 1×, 2×, and 4× threshold current levels to elicit pressor responses. Stimulation of the hypothalamic site produced current-dependent increases in SAP (6–85 mm Hg), in heart rate (3–56 beats/min), and in infrarenal aortic blood flow (0–85 mL/min). Reticular formation site stimulation produced graded increases in SAP (6–129 mm Hg) only. Isoflurane (1.5%, 2.5%, and 3.0%), etomidate (3.0-mg/kg bolus and $0.4\text{-mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ infusion), and midazolam (7.5-mg/kg bolus and $0.2\text{-mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ infusion) were then administered in separate experimental groups. After a steady hemodynamic state was established with each agent, stimulation sequences were repeated. Isoflurane produced an attenuation of the responses of SAP (from 85.1 ± 8.2 to 17.8 ± 6.1 mm Hg at 1.5%, to 7.2 ± 2.0 mm Hg at 2.5%, and to 4.7 ± 2.0 mm Hg at 3%, all $P < 0.05$), heart rate (from 41.1 ± 13.0 to 12.5 ± 2.7 beats/min at 2.5% and to 6.2 ± 1.7 beats/min at 3%, all $P < 0.05$), and of the infrarenal aortic blood flow (from 72.6 ± 14.3 to 11.8 ± 4.2 mL/min at 1.5%, to 10.2 ± 5.6 mL/min at 2.5%, and to 3.2 ± 1.5 mL/min at 3%, all $P < 0.05$) to the highest level of hypothalamic site stimulation. Isoflurane similarly produced an attenuation of the SAP response (from 128.7 ± 10.3 to 15.4 ± 8.1 mm Hg at 1.5%, to 0.2 ± 1.1 mm Hg at 2.5%, and to 0.3 ± 0.5 mm Hg at 3.0%, all $P < 0.05$) to the highest level of reticular formation site stimulation. Etomidate administration attenuated SAP responses to the highest level of hypothalamic site stimulation (from 50.6 ± 6.8 to 24.4 ± 10.8 mm Hg, $P < 0.05$) and to the highest level of reticular formation site stimulation (from 92.7 ± 14.0 to 23.8 ± 12.6 mm Hg). Heart rate and blood flow responses were not changed by etomidate. Similarly, midazolam administration blunted the SAP responses to the highest level of hypothalamic site stimulation (from 73.0 ± 8.9 to 38.0 ± 7.2 mm Hg, $P < 0.05$) and to the highest level of reticular formation site stimulation (from 108.0 ± 17.9 to 54.7 ± 17.7 mm Hg, $P < 0.05$). Blood flow responses were not changed by midazolam, and only heart rate change at the highest level of hypothalamic stimulation was decreased (from 56.7 ± 7.9 to 32.0 ± 6.4 beats/min, $P < 0.05$). During emergence from isoflurane, occasional conversion of pressor to depressor responses was observed. The results suggest that disruption of central nervous system cardiovascular control centers may contribute to the alterations in hemodynamic stability produced by these anesthetic agents.

(Anesth Analg 1991;73:64–75)

Volatile anesthetics, including isoflurane, and intravenous anesthetic agents, such as midazolam and etomidate, have been previously demonstrated to disrupt regulation of the circulation. Postulated mechanisms include direct anesthetic actions on the heart, alterations in arterial and venous sympathetic tone, and changes in circulating catecholamine levels (1). A disruption of central neural control elements, which modulate tonic sympathetic and parasympathetic activities and alterations in baroreceptor reflex function, may also contribute to changes in cardiovascular regulation (2–4).

Isoflurane has been demonstrated to produce dose-dependent decreases in systemic arterial pressure, cardiac output, and systemic vascular resistance, usually in combination with a slight increase in the basal heart rate (1). Isoflurane has also been shown to diminish

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Supported in part by USPHS Grant HL 36144, NIH Anesthesiology Research Training Grant 1T32 GM 08377, and VA Medical Research Funds.

Accepted for publication February 22, 1991.

Address correspondence to Dr. Schmeling, Department of Anesthesiology, Medical College of Wisconsin, MFRC, Room A1000, 8701 West Watertown Plank Road, Milwaukee, WI 53226.

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0003-2999/91/$3.50

sympathetic efferent activity. In contrast, etomidate (a carboxylated imidazole) and midazolam (a benzodiazepine) have been reported to produce minimal alterations in hemodynamics. Previous studies have demonstrated that etomidate produced minimal alterations in systemic arterial pressure, cardiac index, right heart filling pressures, systemic vascular resistance, and heart rate (5). Similarly, midazolam has been shown to have little effect on systemic arterial pressure, heart rate, systemic vascular resistance, ventricular end-diastolic pressure, and indices of left ventricular contractility (6,7). However, whereas peripheral end-organ actions and indices of systemic cardiovascular regulation have been extensively investigated for these agents, few studies have addressed possible disruptions in cardiovascular control mechanisms within the central nervous system (CNS).

Early studies demonstrated that halothane attenuates systemic hemodynamic responses to stimulation of cardiovascular pressor sites in the CNS (8). However, no recent studies have examined the actions of isoflurane, etomidate, and midazolam on such pressor responses to stimulation of CNS sites of cardiovascular control. In addition, most experiments that have examined the hemodynamic effects of anesthetic agents have been conducted in acute, frequently open-chest preparations with a baseline anesthetic. Such experimental conditions result in multiple physiologic alterations including cardiovascular responses to varied preload and afterload (9,10), disruptions in baroreceptor control mechanisms (11,12), altered cardiac force-frequency relationships (13), and disruptions of normal cardiac output and regional myocardial blood flow (14,15). The use of chronically instrumented animals in the present investigation minimized the introduction of experimental artifact.

The purpose of the present investigation was to examine the actions of isoflurane, midazolam, and etomidate on the heart rate, systolic arterial pressure (SAP), infrarenal aortic blood flow, and calculated lower body vascular resistance responses to electrical stimulation of sites of cardiovascular control in the CNS of chronically instrumented cats. Previous studies have identified the ventrolateral hypothalamus and the mesencephalic reticular formation as important CNS cardiovascular control sites (16–19). Electrical stimulation of these sites produces an increase in SAP, sometimes accompanied by an increase in heart rate. Thus, these sites were chosen for study.

Methods

General Preparation

All studies were approved by the Medical College of Wisconsin Animal Welfare Committee, and all procedures and protocols used in these studies conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and were in accordance with NIH guidelines (20). Twenty-three male and female cats (weight, 2.0–3.5 kg; mean, 2.7 kg) were anesthetized by inhalation induction with halothane, then endotracheally intubated, and positive pressure-ventilated. All surgical sites were sterilely prepared and draped, and all procedures were performed under aseptic conditions. The right carotid artery and right external jugular vein were cannulated for pressure measurement and for fluid and drug administration, respectively. A thermocouple was placed in the abdomen through a small incision for measurement of deep core body temperature. All catheters were tunneled subdermally to a lateral thoracic exit site.

During anesthesia, animals were placed in stereotaxic restraint. The skull was exposed through a midline incision. Burr holes through the calvarium were made with a fiberoptic, high-speed, air-turbine drill (Midwest Dental products, Des Plaines, Ill.) Bipolar stimulating electrodes, constructed of twisted 10-mil Formvar-insulated, stainless steel wire, were stereotaxically lowered in 0.5-mm increments toward target sites in the right ventrolateral hypothalamus (Horsely-Clark; anterior, 10.0 mm; lateral, 2.5 mm; depth, −4.0 mm) and left mesencephalic reticular formation (Horsely-Clark; anterior, 2.0 mm; lateral, 2.0 mm; depth, −1.0 mm) according to the atlas of Jasper and Ajmone-Marsan (21). The stimulus for pressor responses was a 10-s train of 0.05–0.1-ms square-wave pulses delivered at 100 Hz through a constant current unit using digital stimulators (WPI Electronics, New Haven, Conn.). After determining the optimal depth for obtaining pressor responses, electrodes were anchored to the skull using acrylic cement and were connected to small 1-72 cap screws contained within a miniature headplate. The headplate was then anchored to the skull using acrylic cement and 0-80 stainless steel screws.

In selected animals ($n = 6$), an incision was made at the midline of the ventral abdomen and the peritoneum was exposed. Careful dissection was done to expose and to isolate the abdominal aorta infrarenally. Either a Statham electromagnetic flow probe (Statham Instruments, Oxnard, Calif.) or Transonic ultrasonic flow probe (Transonic Instruments, Ithaca, N.Y.) was then placed around the aorta and sutured in place. Care was taken to ensure that aortic flow was not restricted. Using an olive probe, the proximal connector was passed subdermally to the thoracic exit site. All flow probes were calibrated in situ postmortem by cannulating the abdominal aorta proximally and distally and by perfusing at known flow rates with heparinized blood.

All wounds were closed in layers. Animals were allowed to recover for a minimum of 7–10 days. After operation, each animal was fitted with a jacket (Alice King Chatham, Los Angeles, Calif.) in a pocket of which were housed arterial and venous catheters. Each animal intramuscularly received 100,000 U of penicillin daily for 3–5 days after implantation. During the postoperative recovery period, each cat was trained to rest quietly in a restraining sling (Alice King Chatham). Arterial and venous catheters were flushed daily with a minimum of heparinized saline solution.

Stimulation of CNS Pressor Sites in the Hypothalamus and Reticular Formation

On the day of experimentation, each cat was placed in the sling, and the following values were monitored and recorded continuously on a Grass polygraph: systemic arterial pressure, pulsatile and mean aortic flow, heart rate, respiration, and deep core body temperature. Stimuli trains were delivered to both the hypothalamic and reticular formation sites, and the SAP responses were assessed. For each site a threshold current, which elicited a small but consistent arterial pressor response, was established. Random stimulus sequences of threshold and 2× and 4× threshold current were then used to elicit a graded series of pressor responses 3–5 min apart. Current intensity was monitored and adjusted continuously during stimulus presentations by means of an optically isolated stimulus current monitor designed and constructed in this laboratory. This ensured that even if electrode impedance varied during the course of an experiment, current density remained the same as the selected control value. Intensity usually varied between 0.01 and 0.05 mA at threshold stimuli. Deep core temperature was maintained during all experiments by selective application of direct current heating pads or heat lamps.

Experimental Protocol

Isoflurane, etomidate, and midazolam were administered on separate days to each animal in a random order.

Isoflurane experiments. After quantitating baseline hemodynamics, establishing control pressor responses, and obtaining baseline blood samples for arterial blood gas tension measurement, isoflurane anesthesia was initiated by a slow, mask inhalational technique. Following endotracheal intubation, positive pressure ventilation was initiated using a semiclosed circuit technique. Inspired anesthetic concentrations of 1.5%, 2.5%, and 3.0% isoflurane in oxygen were then administered in a partial Latin square design. Vaporizers were calibrated through a mass spectrometer (Marquette Electronics, Milwaukee, Wis.).

To provide a hemodynamic steady state, a minimum 30-min equilibration period was allowed to elapse between each change in anesthetic concentration and stimulus presentation. Arterial blood gas tensions were also determined at this time, and ventilation was adjusted as needed to maintain baseline values. Stimuli sequences were randomized, and pressor responses at each inspired concentration of anesthetic were determined. Isoflurane was then discontinued. On emergence and apparent return of consciousness (within 45 min after discontinuing isoflurane), a single 4×-threshold stimulation of both CNS pressor sites was accomplished and hemodynamic alterations were quantitated. Stimulus sequences were repeated 48–72 h after experimentation in all animals to verify the transient nature of the anesthetic action on pressor responses to CNS stimulation.

Etomidate and midazolam experiments. After quantitating baseline hemodynamics, establishing control pressor responses, and obtaining baseline blood samples for arterial gas tensions, etomidate (3.0-mg/kg IV bolus followed by a 0.4-mg·kg^{-1}·h^{-1} infusion) or midazolam maleate (7.5-mg/kg IV bolus followed by 0.2-mg·kg^{-1}·h^{-1} infusion) was administered. Ten to fifteen minutes were allowed for hemodynamic equilibration. Arterial blood gas tensions were also determined at this time, and ventilation was adjusted as needed to maintain baseline values. Central nervous system stimulation sequences were again performed, and the resulting hemodynamic alterations were recorded as in isoflurane experiments.

Histologic Documentation of Electrode Sites

At the conclusion of all experiments, the cats were killed with a lethal dose of pentobarbital and stimulation sites were marked by passing a 5-mA DC current between the tip and the shaft of each electrode for 15 s. The brain was perfused in situ with saline solution followed by 10% formalin-saline solution (vol/vol) and was removed from the skull. The brain was placed in 10% formalin-saline solution containing 0.5% sodium ferrocyanide to complete fixation and to develop Prussian Blue marks at the electrode tip sites. After several days of fixation, brains were blocked, frozen, and sectioned for histologic determination of electrode sites using methods previously described (22).

Table 1. Effects of Isoflurane on Systemic Hemodynamics

						After isoflurane	
	n	Conscious control	1.5% Isoflurane	2.5% Isoflurane	3% Isoflurane	Emergence 30–60 min	48 h
Heart rate (beats/min)	12	218 ± 7	151 ± 15[a]	116 ± 8[a]	108 ± 13[a]	168 ± 13[a]	221 ± 14
Systolic arterial pressure (mm Hg)	12	150 ± 11	90 ± 7[a]	68 ± 3[a]	59 ± 3[a]	159 ± 6	131 ± 4
Mean arterial pressure (mm Hg)	12	114 ± 5	60 ± 7	40 ± 2	35 ± 2	123 ± 5	103 ± 4
Diastolic arterial pressure (mm Hg)	12	95 ± 4	44 ± 7	26 ± 2	22 ± 2	105 ± 5	90 ± 4
Abdominal aortic blood flow (mL/min)	5	107 ± 20	57 ± 10[a]	35 ± 8[a]	31 ± 8[a]	82 ± 13	79 ± 10
Lower body vascular resistance ($\text{mm Hg}\cdot\text{mL}^{-1}\cdot\text{min}^{-1}$)	5	1.14 ± 0.14	1.07 ± 0.15	1.65 ± 0.55	1.67 ± 0.58	1.65 ± 0.28	1.31 ± 0.16

Values are mean ± SEM.

[a] Significantly ($P < 0.05$) different from conscious control values.

Statistical Analysis

Pressor responses were calculated as change in systolic arterial pressure from measurements taken immediately before stimulation of each CNS site. Lower body vascular resistance was calculated as change in mean arterial pressure divided by change in mean aortic blood flow. Hemodynamic responses before and during anesthesia were analyzed with a repeated-measures analysis of variance (23). Pairwise comparisons of interventions were performed with contrasts derived from the repeated-measures analysis of variance, adjusting for multiplicity by Bonferroni's method. All statistical analyses were performed using SAS system software on a VAX mainframe computer. Changes were considered significant when the probability (*P*) value was less than 0.05. All data are expressed as the mean ± SEM.

Results

Alterations in Systemic Hemodynamics Produced by Isoflurane, Etomidate, and Midazolam

Isoflurane typically produced more pronounced effects on hemodynamic values than did etomidate or midazolam. Three animals received only isoflurane and not etomidate or midazolam because of technical problems with instrumentation.

Isoflurane. Isoflurane at 3.0% inspired concentration significantly decreased heart rate by 50% (from 218 ± 7 to 108 ± 5 beats/min), systolic arterial pressure by 61% (from 150 ± 11 to 59 ± 3 mm Hg), mean arterial pressure by 70% (from 114 ± 5 to 34 ± 2 mm Hg), diastolic arterial pressure by 77% (from 96 ± 4 to 22 ± 2 mm Hg), and abdominal aortic blood flow by 71% (from 107 ± 20 to 31 ± 8 mL/min) (Table 1). Calculated lower body vascular resistance increased by 29% at the highest concentration of isoflurane, but this was not significantly different from the control value. The increase in lower body resistance reflected a relatively greater decrease in abdominal aortic blood flow than in systemic arterial pressure.

Etomidate. Etomidate significantly decreased heart rate by 18% (from 235 ± 8 to 193 ± 12 beats/min) and abdominal aortic blood flow by 58% (from 120 ± 26 to 50 ± 11 mL/min). However, systolic, diastolic, and mean arterial pressures were not significantly different from conscious control levels (Table 2). The significant decrease in abdominal aortic blood flow, in combination with minimal alteration in systemic arterial pressure, significantly increased the calculated vascular resistance by 116% (from 1.08 ± 0.18 to 2.34 ± 0.27 $\text{mm Hg}\cdot\text{mL}^{-1}\cdot\text{min}^{-1}$).

Midazolam. Midazolam significantly increased SAP by 12% (from 127 ± 8 to 143 ± 7 mm Hg), mean arterial pressure by 20% (from 98 ± 6 to 118 ± 5 mm Hg), and diastolic arterial pressure by 27% (from 83 ± 5 to 105 ± 5 mm Hg). However, no significant alterations in heart rate, aortic flow, or vascular resistance were observed (Table 3).

Conscious Control Responses to Stimulation of Pressor Sites in the Hypothalamus and Reticular Formation

Stimulation of the ventrolateral hypothalamic or mesencephalic reticular formation sites in the CNS pro-

Table 2. Change in Systemic Hemodynamics Produced by Etomidate (3.0-mg/kg bolus, 0.4-mg·kg^{-1}·h^{-1} infusion)

	n	Conscious control	Etomidate	48 h after etomidate
Heart rate (beats/min)	9	235 ± 8	193 ± 12*	238 ± 11
Systolic arterial pressure (mm Hg)	9	140 ± 7	133 ± 8	129 ± 78
Mean arterial pressure (mm Hg)	9	111 ± 5	108 ± 7	99 ± 5
Diastolic arterial pressure (mm Hg)	9	96 ± 4	95 ± 7	84 ± 5
Abdominal aortic blood flow (mL/min)	4	120 ± 26	50 ± 11*	119 ± 23
Lower body vascular resistance (mm Hg·mL^{-1}·min^{-1})	4	1.08 ± 0.18	2.34 ± 0.27*	1.09 ± 25

Values are mean ± SEM.
*Significantly ($P < 0.05$) different from conscious control values.

Table 3. Changes in Systemic Hemodynamics Produced by Midazolam (7.5-mg/kg bolus, 0.2-mg·kg^{-1}·h^{-1} infusion)

	n	Conscious control	Midazolam	48 h after midazolam
Heart rate (beats/min)	9	232 ± 11	233 ± 14	232 ± 11
Systolic arterial pressure (mm Hg)	9	127 ± 8	143 ± 7*	137 ± 9
Mean arterial pressure (mm Hg)	9	98 ± 6	118 ± 5*	107 ± 6
Diastolic arterial pressure (mm Hg)	9	83 ± 5	105 ± 5*	92 ± 5
Abdominal aortic blood flow (mL/min)	4	113 ± 24	94 ± 19	129 ± 43
Lower body vascular resistance (mm Hg·mL^{-1}·min^{-1})	4	1.01 ± 0.12	1.4 ± 0.23	1.2 ± 0.32

Values are mean ± SEM.
*Significantly ($P < 0.05$) different from conscious control values.

duced graded alterations in hemodynamic responses (Figures 1–3, Table 4). Reticular formation stimulation was associated with greater current-dependent increases in SAPs than was stimulation of hypothalamic sites (Figures 1–3, Table 4). Additionally, the increases in SAP produced by stimulation of reticular formation sites were not associated with alterations in either heart rate or abdominal aortic blood flow (Tables 5 and 6). In contrast, hypothalamic stimulation resulted in graded positive chronotropic actions on the heart and in increases in abdominal aortic blood flow, concurrent with the increases in SAPs (Tables 5 and 6).

Effects of Isoflurane, Etomidate, and Midazolam on Stimulation of Pressor Sites in the CNS

Isoflurane. Isoflurane produced a dose-dependent attenuation of the arterial pressor response to all levels of hypothalamic and reticular formation stimulation (Figure 1, Table 4). The highest concentration of isoflurane (3.0%) essentially abolished pressor responses at all stimulus intensities. Although an increase in abdominal aortic blood flow resulted after hypothalamic stimulation in conscious control ani-

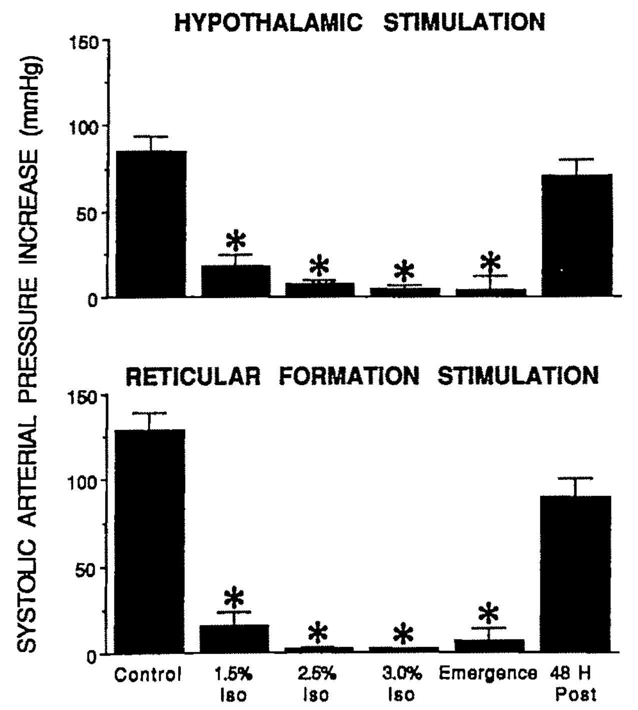

Figure 1. Effects of isoflurane (1.5%, 2.5%, 3.0%) administration on systolic arterial pressure response to 4× threshold hypothalamic and reticular formation site stimulation. Data expressed as mean ± SEM. *Significantly different ($P < 0.05$) from conscious control responses.

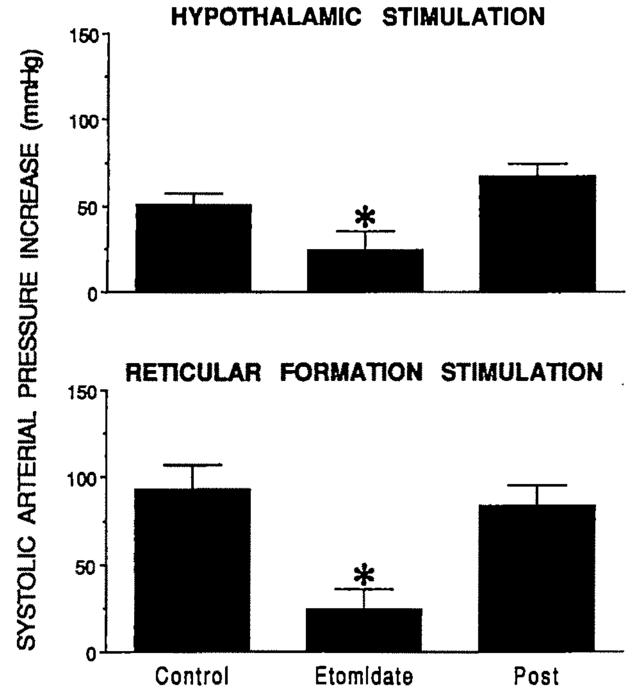

Figure 2. Effects of etomidate (3.0-mg/kg bolus and 0.4-mg·kg^{-1}·h^{-1} infusion) on systolic arterial pressure response to 4× threshold hypothalamic and reticular formation site stimulation. Data expressed as mean ± SEM. *Significantly different ($P < 0.05$) from conscious control responses.

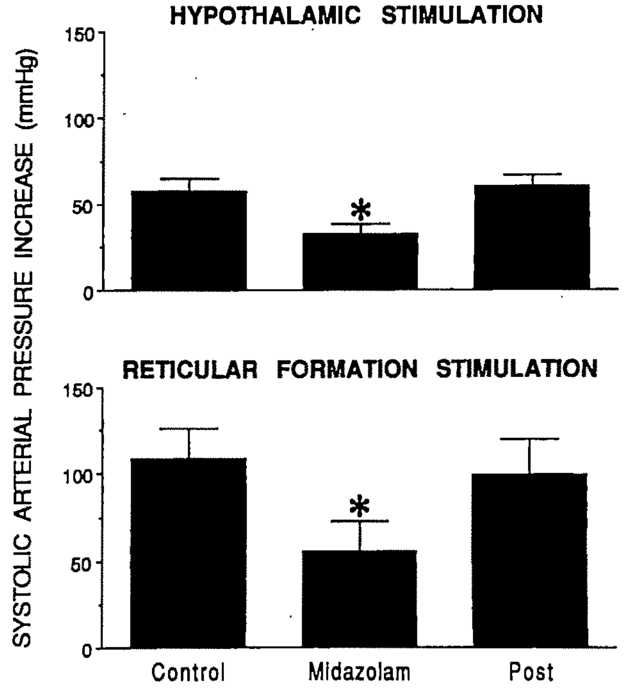

Figure 3. Effects of midazolam on systolic arterial pressure response to 4× threshold hypothalamic and reticular formation site stimulation. Data expressed as mean ± SEM. *Significantly different ($P < 0.05$) from conscious control responses.

mals, this response was attenuated by isoflurane (Table 6). Similarly, positive chronotropic actions produced by hypothalamic stimulation in the conscious state were attenuated by isoflurane (Table 5).

During emergence from isoflurane, stimulation of either CNS pressor site paradoxically resulted in a decrease (−20 ± 11 mm Hg) in SAP on eight occasions in five cats: in one cat after hypothalamic stimulation only, in two cats after reticular formation stimulation only, and in two cats after either hypothalamic or reticular formation stimulation. Figure 4 demonstrates such paradoxical conversion of pressor to depressor response during emergence from isoflurane anesthesia.

Etomidate. Etomidate significantly attenuated the increase in arterial pressure after stimulation of either hypothalamic or reticular formation sites (Figure 2, Table 4). The positive chronotropic action on the heart and the increases in abdominal aortic blood flow produced by stimulation of hypothalamic sites in the conscious state were not significantly different from that of control (Tables 5 and 6). Calculated vascular resistance increased significantly during stimulation after etomidate. This reflected a greater increase in the arterial pressure than in the abdominal aortic blood flow after CNS stimulation.

Midazolam Midazolam administration was also associated with significant attenuation of the arterial pressure pressor response to stimulation of either the reticular formation or hypothalamic sites (Figure 3, Table 4). As with etomidate, blood flow responses were not changed and only the heart rate increase at the highest level of hypothalamic stimulation was attenuated. Figure 5 illustrates typical effects of midazolam on systemic hemodynamic responses to stimulation of hypothalamic and reticular formation sites.

Histologic Documentation of Electrode Sites

Histologic documentation of electrode sites in the present investigation is graphically portrayed in Figure 6 for placements in the ventrolateral hypothalamus and in Figure 7 for the mesencephalic reticular formation. Hypothalamic sites were located in areas of the ventrolateral hypothalamus adjacent to the third ventricle extending caudally to the mammillotegmental tract and rostrally encompassing a small portion of the mammillothalamic tract (Figure 6). Reticular formation sites were located just lateral to the periacqueductal gray area extending and including the central tegmental field at the level of the nucleus of the oculomotor nerve (Figure 7).

Table 4. Systolic Arterial Pressure Increase During Central Nervous System Stimulation

	Isoflurane (n = 12)					Etomidate (n = 9)			Midazolam (n = 9)		
CNS site stimulation	Control (mm Hg)	1.5%	2.5%	3.0%	Post	Control (mm Hg)	3.0 mg/kg	Post	Control (mm Hg)	7.5 mg/kg	Post
Hypothalamic											
1×	6.3	0.2	0.3	0.0	6.8	5.6	−0.6	8.6	8.0	2.6	5.3
	±0.9	±0.2[a]	±0.3[a]	±0.0[a]	±0.6	±0.3	±1.4[a]	±2.6	±1.4	±0.8[a]	±0.3
2×	27.9	5.9	1.9	0.7	22.8	17.2	7.4	23.4	17.3	11.0	21.7
	±3.3	±2.2[a]	±0.5[a]	±0.5[a]	±0.5	±3.6	±2.1[a]	±2.4	±1.6	±1.8[a]	±2.8
4×	85.1	17.8	7.2	4.7	69.8	50.6	24.4	67.0	73.0	38.0	54.5
	±8.2	±6.1[a]	±2.0[a]	±2.0[a]	±9.9	±6.8	±10.8[a]	±7.6	±8.9	±7.2[a]	±10.3
Reticular formation											
1×	5.7	−0.1	0.0	0.0	8.5	5.7	1.0	5.2	6.2	1.0	7.0
	±0.6	±0.1[a]	±0.0[a]	±0.0[a]	±1.1[a]	±0.6	±0.5[a]	±1.8	±1.0	±0.9	±1.0
2×	46.2	4.1	−0.1	0.0	34.2	20.4	0.8	19.6	35.1	9.8	26.1
	±2.8	±2.5[a]	±0.2[a]	±0.0[a]	±7.1	±3.3	±2.3[a]	±3.1	±7.3	±3.0[a]	±4.8
4×	128.7	15.4	0.2	0.3	89.5	92.7	23.8	83.2	108.0	54.7	98.6
	±10.3	±8.1[a]	±1.1[a]	±0.5[a]	±10.6	±14.0	±12.6[a]	±11.0[a]	±17.9	±17.7[a]	±20.6

1× stimulus intensity represents threshold stimulation.
[a] Significantly different from control values ($P \le 0.05$).

Table 5. Heart Rate Change During Central Nervous System Stimulation

	Isoflurane (n = 12)					Etomidate (n = 9)			Midazolam (n = 9)		
CNS site stimulation	Control (beats/min)	1.5%	2.5%	3.0%	Post	Control (beats/min)	3.0 mg/kg	Post	Control (beats/min)	7.5 mg/kg	Post
Hypothalamic											
1×	4	0.7	−0.1	0.5	−4.6	3.1	−4.3	8.3	5.3	0.0	8.8
	±4	±0.4	±0.4	±0.5	±3.3	±4.1	±2.7	±6.7	±3.4	±1.8	±3.9
2×	3.2	6.2	2.7	1.8	−14.0	17.6	−1.6	22.0	21.2	4.8	29.3
	±13.4	±2.5	±0.8	±1.0	±13.9	±7.83	±4.9	±5.8	±2.7	±4.0	±10.8
4×	41.1	24.3	12.5	6.2	23.3	39.4	25.3	43.8	56.7	32.0	60.0
	±13.0	±8.2	±2.7[a]	±1.7[a]	±31.9	±11.1	±17.3	±8.7	±7.9	±6.4[a]	±6.3
Reticular formation											
1×	6.5	0.6	0.2	0.0	−5.0	−4.6	0.0	−0.3	−0.4	0.1	−4.4
	±4.9	±0.6	±0.2	±0.0	±3.0	±4.5	±2.3	±2.0	±3.3	±3.3	±3.5
2×	7.6	5.2	−0.6	−0.3	4.4	70.7	−5.5	4.3	12.4	1.3	3.6
	±12.1	±3.9	±0.5	±0.2	±10.3	±9.0	±3.9	±5.9	±8.1	±10.5	±10.5
4×	19.2	6.6	0.7	0.0	8.8	13.0	−19.6	18.0	26.2	5.0	16.0
	±21.4	±7.3	±2.5	±0.8	±20.2	±20.7	±13.4	±20.9	±18.6	±10.0	±24.0

1× stimulus intensity represents threshold stimulation.
[a] Significantly different from control values ($P \le 0.05$).

Discussion

The purpose of the present investigation was to examine the effects of three anesthetic agents on systemic hemodynamics after the stimulation of cardiovascular control centers in ventrolateral hypothalamic and mesencephalic reticular formation sites. The results are consistent with the disruptive actions of isoflurane, etomidate, and midazolam at these CNS levels. Autonomic responses, including hemodynamic alterations, to electrical stimulation of discrete CNS sites were first described in 1909 (24,25). Subsequent investigations have documented a variety of neuronal pathways between these CNS sites and end-organ mediators of these responses. Degeneration studies of documented hypothalamic pressor sites have implicated at least two descending pathways: a lateral path traversing bulbospinal areas and terminating in the intermediomedial and intermediolateral nuclei of the spinal cord at C-8 to T-12 levels, and a more medial path, which partly terminates caudally in brainstem areas including the

Table 6. Infrarenal Aortic Blood Flow Change During Central Nervous System Stimulation

	Isoflurane (n = 4)					Etomidate (n = 4)			Midazolam (n = 4)		
CNS site stimulation	Control (mL/min)	1.5%	2.5%	3.0%	Post	Control (mL/min)	3.0 mg/kg	Post	Control (mL/min)	7.5 mg/kg	Post
Hypothalamic											
1×	7.0	0.6	2.6	0.4	−8.0	0.3	−0.2	0.0	7.0	1.2	15.7
	±1.9	±0.5^a	±1.4^a	±0.4^a	±5.8	±2.3	±1.6	±6.3	±6.2	±5.6	±6.1
2×	23.4	28.0	3.6	1.0	24.0	28.5	−0.5	33.7	29.7	5.2	−3.6
	±9.6	±1.6^a	±1.6^a	±0.9^a	±14.9	±18.6	±6.2	±16.3	±15.6	±9.8	±27.1
4×	72.6	11.8	10.2	3.2	36.3	66.0	−1.7	88.0	84.5	37.2	68.0
	±14.3	±4.2^a	±5.6^a	±1.5^a	±21.8	±41.2	±4.0	±21.9	±15.9	±28.2	±17.5
Reticular formation											
1×	−3.6	−1.0	0.0	0.0	−1.7	−2.2	3.2	−4.2	−7.7	−3.5	4.0
	±4.0	±0.6	±0.0	±0.0	±3.9	±6.4	±3.0	±5.6	±6.7	±5.0	±7.5
2×	17.2	−1.0	−0.4	−0.4	20.7	−13.0	−4.0	12.2	11.5	−9.0	4.3
	±16.4	±2.0	±0.4	±0.4	±13.0	±14.6	±4.5	±16.0	±22.3	±9.9	±21.4
4×	28.8	2.8	−0.4	−0.4	32.6	28.5	−5.5	27.7	−14.5	−24.0	−15.0
	±39.6	±5.6	±1.4	±0.4	±36.8	±46.0	±14.0	±33.3	±47.0	±22.2	±44.5

1× stimulus intensity represents threshold stimulation.
[a]Significantly different from control values ($P \leq 0.05$).

accessory cuneate nucleus, the nucleus tractus solitarius, and parahypoglossal regions (18).

The nucleus tractus solitarius has been demonstrated as a termination site of various cardiovascular afferents including the carotid sinus baroreceptor (26,27). Synaptic connections between the parahypoglossal region and the intermediolateral nucleus of the spinal cord have been demonstrated electrophysiologically (28). As the intermediolateral nucleus is the site of origin of many sympathetic preganglionic neurons projecting to postganglionic sympathetic vasoactive neurons innervating both the peripheral vasculature and adrenal glands (29), the attenuation of the pressor responses to stimulation of ventrolateral hypothalamic sites after isoflurane, etomidate, or midazolam may represent an action at one of several CNS sites. Disruption of traffic in various cardiovascular afferents, including the baroreceptor arc, could tonically alter modulation of CNS cardiovascular centers. A change in the responsiveness of CNS cardiovascular centers after anesthesia could alter the effects of central stimulation. Altered responses in more peripheral neuronal tracts including pre- and postganglionic neurons could attenuate pressor responses secondary to CNS stimulation. Finally, the precise site of action may be difficult to determine as these agents have direct effects on the heart and peripheral vasculature. Previous studies have attempted to address this question with various anesthetics including halothane.

Price et al. (30), using acute pentobarbital-anesthetized dogs, delivered 1%–2% halothane to the purported isolated cephalic circulation only, and demonstrated decreases in arterial pressure, heart rate, and cardiac contractile force and reduced hemodynamic responses to carotid sinus occlusion. The conclusion of this study was that the clinical hemodynamic effects observed with halothane result from a central depression of normal cardiovascular homeostatic pathways. This CNS depression would allow the anesthetic to produce direct effects on the heart and the peripheral vasculature without compensatory neuronal buffering reflexes. Further evidence for actions of volatile anesthetics at CNS cardiovascular control centers was provided by Price et al. (31) in a vagotomized decerebrate dog model. This study examined the effects of local microinjection of halothane, cyclopropane, and procaine at previously identified medullary pressor and depressor sites. Halothane, cyclopropane, and 2% procaine, but not 1% procaine or saline solution, caused reversible inhibition of the normal pressor and depressor responses.

In the present investigation, the administration of isoflurane caused a marked blunting of all hemodynamic responses resulting from graded stimulation of ventrolateral hypothalamic sites. In contrast, etomidate and midazolam significantly attenuated the systolic arterial pressure responses to stimulation but not the positive chronotropic or abdominal aortic flow responses. The results with etomidate and midazolam are consistent with a diminished sensitivity of CNS cardiovascular centers, with less depressant peripheral actions on peripheral cardiovascular elements than isoflurane. On the other hand, higher doses of these drugs may have displayed actions similar to isoflurane. The present results, however, are consistent with previous studies demonstrating

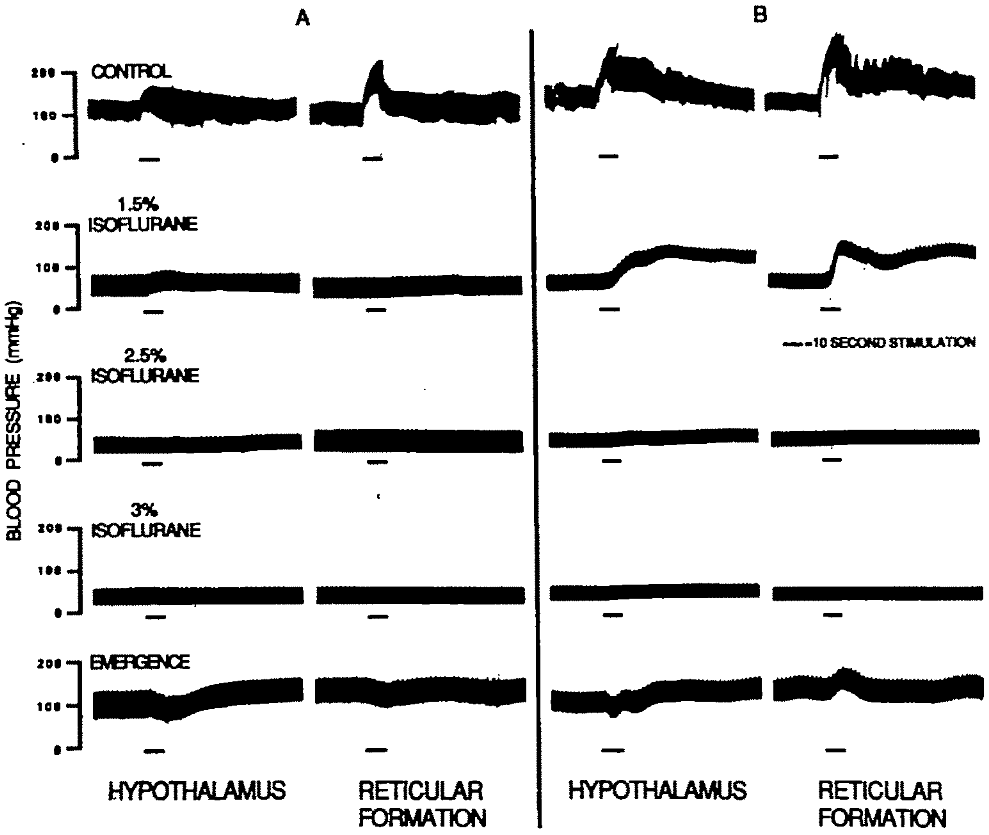

Figure 4. Effect of isoflurane on systemic arterial pressure responses to hypothalamic and reticular formation site stimulation in two chronically instrumented cats: No. 9 (A); and No. 13 (B). Note the marked blunting of arterial pressure responses to stimulation during high concentrations of isoflurane. During emergence, note the appearance of depressor responses to hypothalamic (A+B) and reticular formation (A) site stimulation.

greater cardiovascular stability with etomidate and midazolam than with volatile anesthetics (3,5–7).

The pressor responses evoked in the present study require both intact neuronal pathways and a normal cardiovascular system. In the present investigation, the direct actions of the anesthetic agents on the heart and peripheral vasculature were not quantified. Direct negative inotropic and chronotropic actions on the heart, relaxation of vascular smooth muscle, and actions on sympathetic and parasympathetic ganglia have been previously demonstrated for these agents (1–3,32) and may have contributed to the observed results. However, the results of the current investigation, in conjunction with previous results regarding effects on end-organ mediators and CNS sites, are consistent with a nonspecific depression by isoflurane of neural control elements. Such depression of cardiovascular neuronal reflexes allows peripheral vascular actions of the anesthetic to be more pronounced.

The attenuation of pressor responses to CNS stimulation with minimal alterations in heart rate or aortic blood flow responses produced by etomidate or midazolam is consistent with a more selective action of these agents on cardiovascular neural control centers with residual preservation of baroreceptor reflex arcs. As the hypothalamic stimulation site and associated pathways have been previously demonstrated to monosynaptically modulate tonic sympathetic discharge (33), such action may represent a suprabulbar influence on the baroreceptor reflex arc. Previous studies have demonstrated that midazolam and etomidate minimally disrupt normal baroreceptor-mediated cardiovascular reflexes (3,4). Differential degrees of tonic sympathetic efferent activity to peripheral vasculature and to the adrenal glands and/or alterations in afferent control elements may also contribute to these differences between agents (1,3,12).

The partial preservation of reflex responses and the consequent cardiovascular homeostasis produced by etomidate and midazolam appear different from that produced by isoflurane. Previous studies suggest that isoflurane may preserve baroreflex control mechanisms and maintain sympathetic efferent outflow to a greater extent than other volatile anesthetic agents (1–2). However, when comparing the hemodynamic consequences of etomidate or midazolam with isoflurane anesthesia, such a therapeutic advantage is

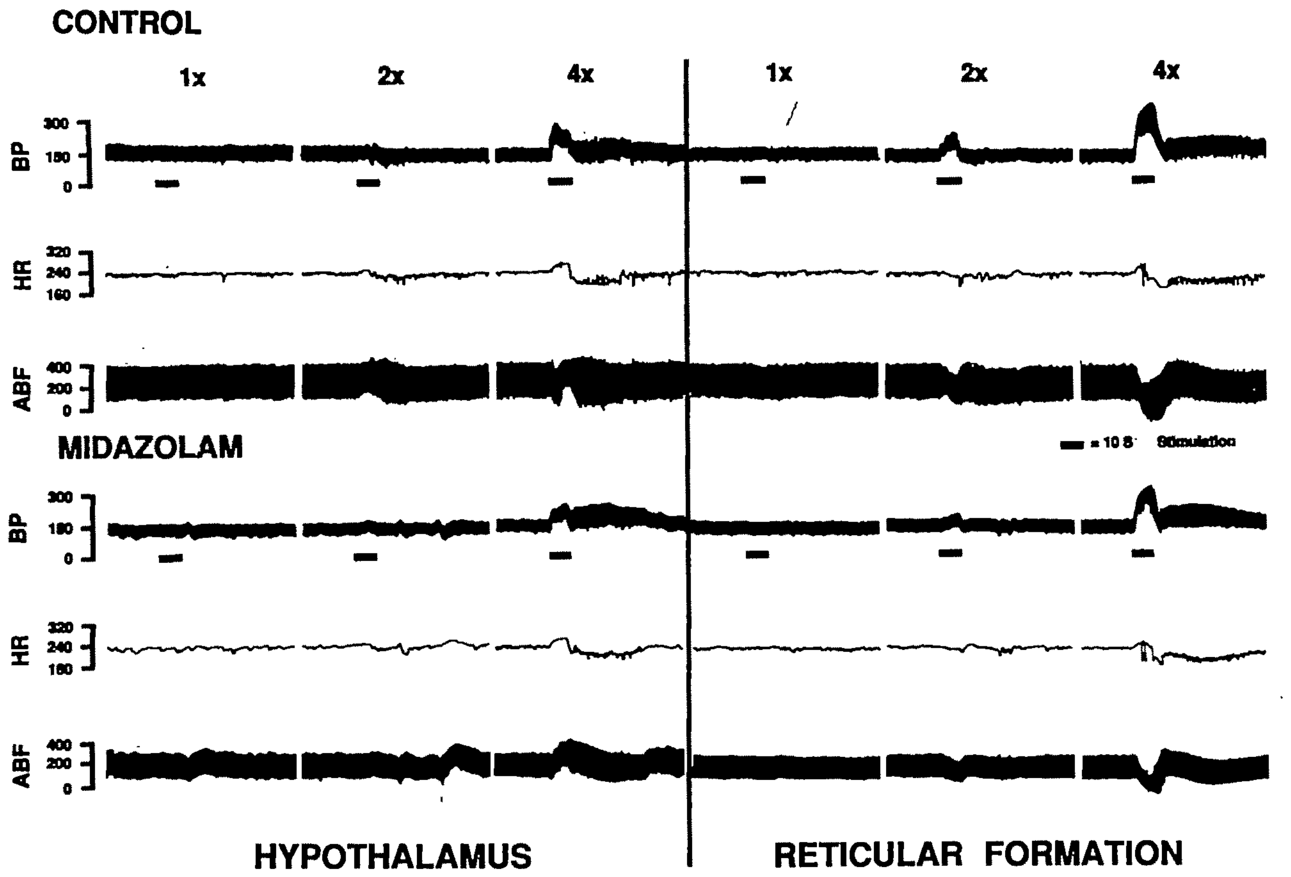

Figure 5. Effects of midazolam (7.5-mg/kg bolus, 0.2-mg·kg^{-1}·h^{-1} infusion) on systemic arterial pressure, heart rate, and infrarenal aortic blood flow responses to hypothalamic and reticular formation site stimulation in a chronically instrumented cat. [HR, heart rate (beats/min); BP, systemic arterial pressure (mm Hg); ABF, infrarenal blood flow (mL/min); 1×, 2×, 4× threshold stimulation and 2× and 4× threshold current, respectively]. Note the significant attenuation of the pressor response after stimulation of either site with a decrease in the corresponding reflex heart rate change after administration of midazolam.

not evident (1–7). In the present study, the ability of midazolam and etomidate, in contrast to isoflurane, to preserve pressor responses supports these previous clinical and experimental observations (1–7).

Anesthetic agents have been previously suggested to produce unconsciousness by depressing neural activity in the mesencephalic reticular formation (34). Descending pathways from the mesencephalic reticular formation involved in cardiovascular regulation have been less well defined than those from the hypothalamus, but include diffuse polysynaptic projections to preganglionic sympathetic neurons in the spinal cord (33). Neurons in the lateral reticular formation have been demonstrated to modulate ascending pathways crucial to the maintenance of consciousness (35–37). Previous studies have suggested that anesthetics suppress excitatory responses and potentiate inhibitory responses mediated at this level. The significant attenuation of pressor responses to stimulation of reticular formation sites after administration of isoflurane, etomidate, or midazolam is consistent with such a suppression of excitatory neural transmission at this level.

The observed conversion of pressor to depressor responses during emergence from isoflurane merits further comment. A previous study (8) demonstrated occasional conversion of pressor to depressor responses at 1%–1.5% halothane. An artifactual explanation is possible as previous studies have demonstrated close proximity of pressor and depressor regions (30,38). It is conceivable that blood pressure and cerebral blood flow changes during emergence from isoflurane could have caused brain movement of a depressor region into closer proximity to the stimulating electrode. Another possible explanation is a facilitation of inhibitory input to cardiovascular control sites. Shimoji et al. (34) in a study of the effect of anesthetics on responses of mesencephalic reticular formation neurons noted that whereas intravenous barbiturates consistently attenuated inhibitory responses of reticular formation neurons, inhalation agents (halothane and isoflurane) at times enhanced

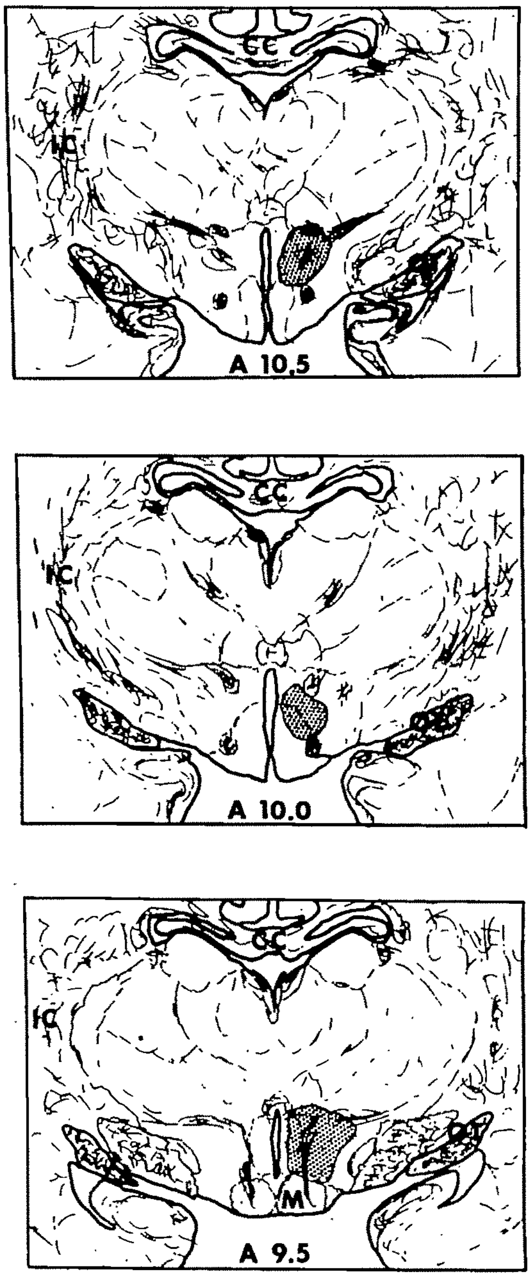

Figure 6. Histologic verification of electrode tip sites for hypothalamic stimulation. Plates correspond to Horsely-Clark coordinates in frontal plane anterior: 9.5, 10.0, and 10.5 mm. (CC, corpus callosum; IC, inferior colliculus; OT, optic tract; M, anterior mammillary nucleus.)

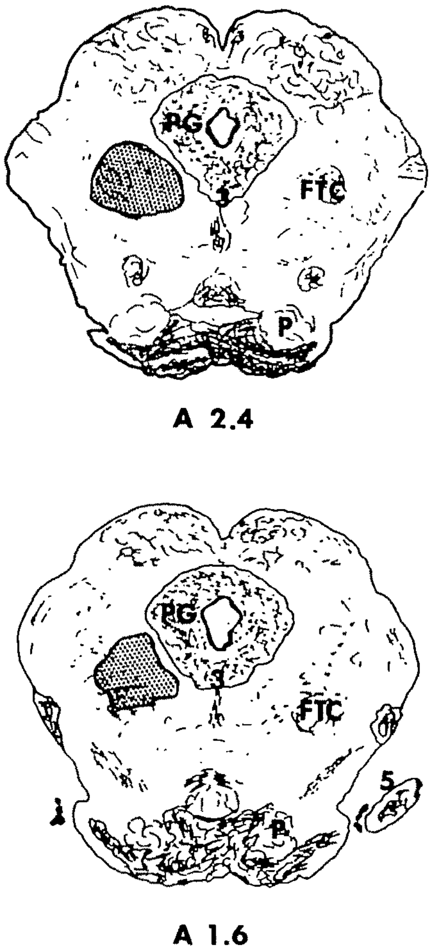

Figure 7. Histologic verification of electrode tip sites for mesencephalic reticular formation stimulation. Plates correspond to Horsely-Clark coordinates in the frontal plane anterior: 1.6 and 2.4 mm. (PG, periacqueductal gray; FTC, central tegmental field; P, pyramidal tract; 3, nucleus of oculomotor nerve; 5, trigeminal nerve.)

such inhibitory responses. Excitatory responses were consistently attenuated by all agents. Hence, it is possible that at some low residual concentrations of isoflurane, a selective blunting of excitatory-relative-to-inhibitory transmission was produced, resulting in vasodepression.

In summary, two CNS sites resulting in profound cardiovascular responses were identified in chronically instrumented cats. Stimulation of a ventrolateral hypothalamic site resulted in increases in systolic arterial pressure, heart rate, and aortic blood flow. Stimulation of sites in the mesencephalic reticular formation also resulted in increases in arterial pressure. Administration of isoflurane dose-dependently attenuated the responses of arterial pressure, heart rate, and blood flow to CNS stimulation. Although etomidate and midazolam reduced the pressor response, they did not reduce the heart rate or blood flow responses to hypothalamic stimulation. During emergence from isoflurane, conversion of pressor to depressor responses was occasionally observed. In conjunction with previous studies of general anesthetic agents, these results are consistent with global inhibition of CNS cardiovascular control sites by isoflurane, with a more selective inhibition of neural control pathways by etomidate and midazolam.

We extend our appreciation to David Schwabe for technical assistance, to Mimi Mick and Evonne Cunningham for preparation of the manuscript, and to David Warltier, MD, PhD for his critical comments.

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Combined Effects of Volatile Anesthetics and Phosphodiesterase Inhibitors on Contractile Performance in Guinea Pig Hearts

Herbert M. Himmel, MD, Thomas Schappert, and Ursula Ravens, PhD
Department of Pharmacology, University of Essen, Essen, Germany

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The cardiotonic effects of the phosphodiesterase inhibitors amrinone, milrinone, and 3-isobutyl-1-methylxanthine were studied in Langendorff-perfused guinea pig hearts exposed to the cardiodepressant concentrations of halothane or isoflurane. Left ventricular pressure, rate of change of pressure (dP/dt), heart rate, and perfusion pressure were measured in the presence of increasing drug concentrations. Under control conditions, both $(dP/dt)_{max}$ and heart rate were increased most with 3-isobutyl-1-methylxanthine and least with amrinone. In isoflurane-pretreated hearts (1.3%, vol/vol), the phosphodiesterase inhibitors increased $(dP/dt)_{max}$ to a larger degree, whereas the increase in heart rate remained similar to that in the control hearts. After exposure to halothane (0.8%, vol/vol), however, amrinone and milrinone were less effective with respect to enhancement of contractile performance. There was no difference in the 3-isobutyl-1-methylxanthine–induced increase of $(dP/dt)_{max}$ between hearts exposed to isoflurane and those exposed to halothane. Our results suggest that contractile performance of isolated hearts is more easily stimulated by milrinone and amrinone in the presence of isoflurane than in the presence of halothane.

(Anesth Analg 1991;73:76–82)

Both halothane and isoflurane depress cardiac force of contraction. In isolated heart muscle, equianesthetic concentrations of halothane and isoflurane have similar negative inotropic effects. However, when active tension is enhanced by potentiating patterns of electrical stimulation, isoflurane has less negative inotropic action than halothane (1,2). We have shown previously that isoflurane is also less cardiodepressant when isolated muscles are stimulated by inotropic drugs (unpublished result).

In a clinical setting, the reverse order of application may be of greater interest. Thus the question arises whether heart muscle that has been exposed to the negative inotropic action of volatile anesthetics still responds to the positive inotropic action of cardiotonic drugs, and, if so, whether this response varies with the anesthetics used. We have addressed this problem by studying the positive inotropic effect of the phosphodiesterase (PDE) inhibitors amrinone, milrinone, and 3-isobutyl-1-methylxanthine (IBMX) in Langendorff-perfused guinea pig hearts, the contractile performance of which had been depressed either by halothane or by isoflurane.

Methods

Langendorff-Perfused Hearts

The coronary vascular bed of isolated hearts of male guinea pigs (body weight, 250–350 g) was perfused through an aortic cannula at a constant flow of 5 mL/min with modified Tyrode's solution of the following composition (in mmol/L): NaCl, 126.7; KCl, 5.4; $CaCl_2$, 1.8; $MgCl_2$, 1.05; NaH_2PO_4, 0.42; $NaHCO_3$, 11.9; glucose, 5.0; and ascorbic acid, 0.06. The aortic cannula was connected to two reservoirs of Tyrode's solution, the first of which was equilibrated with carbogen (95% O_2, 5% CO_2) and the second of which with a mixture of either carbogen plus isoflurane or carbogen plus halothane. The temperature was 32°C and the pH 7.4. Equianesthetic concentrations, i.e., 1 MAC, of halothane (0.8%, vol/vol) or of isoflurane (1.3%, vol/vol) were delivered to the second reservoir by means of the respective Vapor 19.1 (Drägerwerk, Lübeck, Germany). The concentration of the anesthetics in the gas mixture was continuously measured with an IRIS instrument (Drägerwerk), appropriate adjustments at the vapors being made as necessary. The perfusion pressure (PP) was measured with a Statham P23Db cell and continuously registered with a Hellige recorder. The contrac-

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Accepted for publication February 20, 1991.

Address correspondence to Dr. Ravens, Pharmakologisches Institut, Hufelandstrasse 55, D-4300 Essen 1, Germany.

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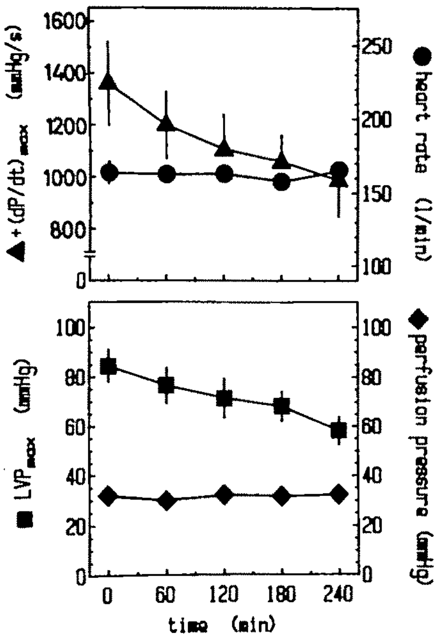

Figure 1. Time dependence of LVP_{max} (*squares*), its derivative $+(dP/dt)_{max}$ (*triangles*), spontaneous HR (*circles*), and PP (*diamonds*) in guinea pig Langendorff-perfused hearts exposed neither to volatile anesthetics nor to PDE inhibitors. Time = 0 is after 90 min of equilibration of the hearts. Mean values ± SEM of five experiments. For $+(dP/dt)_{max}$, there is a statistically significant decrease at time = 180 min, for LVP_{max} at time = 60 min ($P < 0.05$; Student's *t*-test for paired data).

tile performance of the hearts was determined by means of an H_2O-filled latex balloon inserted into the left ventricle. The latex balloon was connected with a piezoelectric pressure transducer (type 501852/8, Braun Melsungen, Melsungen, Germany). The left ventricular pressure (LVP) and the electronically differentiated rate of pressure development (dP/dt) were continuously measured with a model 13-4615-50 transducer amplifier and a model 15-4615-71 differentiator amplifier (cutoff frequency set at 30 Hz) and registered with a model 2202 chart recorder (all Gould Electronics, Cleveland, Ohio). Furthermore, the spontaneous heart rate (HR) was also determined every 10 min. The Langendorff-perfused hearts were equilibrated for at least 90 min with carbogen, followed by 20 min of equilibration with either carbogen plus isoflurane or carbogen plus halothane and then exposed to cumulatively increasing concentrations of the PDE inhibitors (20 min per concentration, steps of 0.5 log units) in the presence or absence of the volatile anesthetics. This was followed by one or two washout periods of 60-min duration each, the first to remove the PDE inhibitor and the second to remove the volatile anesthetic. At the end of each of these periods, the data for PP, HR, LVP_{max}, and its first derivative $(dP/dt)_{max}$ were collected for further evaluation.

Drugs and Solutions

Isoflurane (Forane) was from Abbott (Wiesbaden, Germany), and halothane (Fluothane) from ICI-Pharma (Plankstadt, Germany). Milrinone and amrinone (Wincoram, solution ready for injection) were kindly provided by Winthrop GmbH (Norderstedt, Germany). 3-Isobutyl-1-methylxanthine was purchased from Sigma (Munich, Germany). All other chemicals were from Merck (Darmstadt, Germany). Appropriate dilutions of amrinone from the Wincoram ampoules were prepared fresh every day; milrinone was dissolved in 2 mL of H_2O plus several drops of 6 N HCl and diluted to 20 mL with Tyrode's solution to yield a stock solution of 10^{-2} mol/L; both amrinone and milrinone were always kept protected from light. 3-Isobutyl-1-methylxanthine was dissolved in 360 µL of NaOH and diluted to 6 mL with H_2O, which gave a stock solution of 10^{-3} mol/L.

Data Analysis

Whenever possible, data were expressed as mean values ± SEM of five to seven experiments. Differences between grouped or paired data were evaluated statistically by means of Student's *t*-test or the nonparametric H-test and considered statistically significant if $P < 0.05$ (3).

Results

To assess the contractile performance of the Langendorff-perfused hearts in time-matched controls, we measured LVP, dP/dt, HR, and PP after an initial equilibration period of 90 min. Figure 1 shows these data over the course of experimentation. The contractile performance of the hearts slowly declined with time as documented by the decrease in LVP_{max} and $(dP/dt)_{max}$. These changes became statistically significant after 180 min of perfusion for $(dP/dt)_{max}$ and after 60 min of perfusion for LVP_{max}. Heart rate and PP remained constant. The absolute values were in a similar order of magnitude as described in the literature (for review, see Reference 4).

When IBMX, milrinone, or amrinone was added cumulatively to the perfusion medium in concentration steps of 0.5 log units, the hearts responded with characteristic changes (Figure 2). All three PDE inhibitors significantly increased HR: in the concentration range studied, IBMX accelerated HR by more than 120 beats/min, milrinone by 60 beats/min, and amrinone by 30 beats/min. The increase in $(dP/dt)_{max}$ was greatest with IBMX, intermediate with milrinone, and least with amrinone. With the latter two drugs, the maximum positive inotropic effect was reached

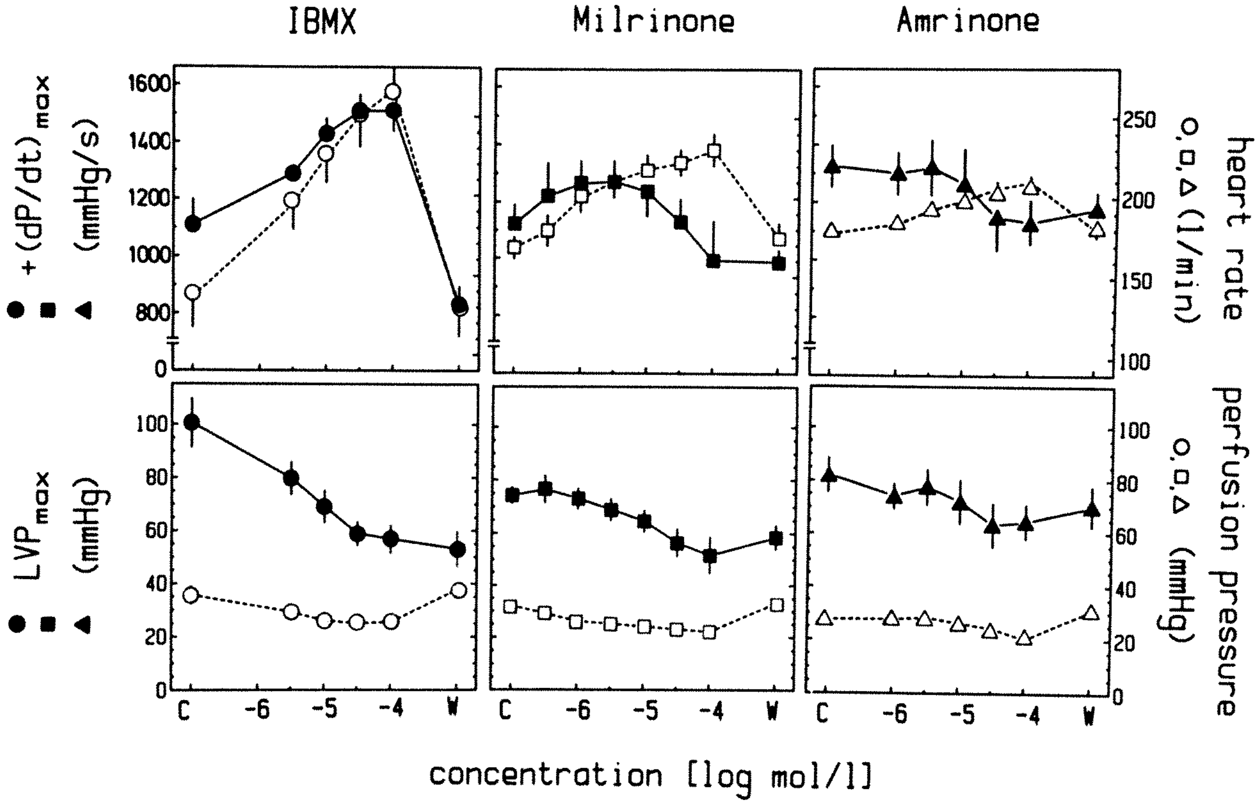

Figure 2. Concentration-response curves for the effects of IBMX, milrinone, and amrinone in Langendorff-perfused hearts in the absence of volatile anesthetics. +(dP/dt)$_{max}$ in mm Hg/s (*filled symbols*) and spontaneous HR in beats/min (*open symbols*) are depicted in the upper row; LVP$_{max}$ in mm Hg (*filled symbols*) and PP in mm Hg (*open symbols*) in the lower row. Abscissas: concentration of PDE inhibitor in log units (mol/L); C and W indicate predrug control values and values obtained after washout of PDE inhibitor, respectively. Mean values ± SEM from five to seven hearts.

with 3 μmol/L. The HR still continued to increase at concentrations that no longer enhanced the absolute values of (dP/dt)$_{max}$. The maximum left ventricular pressure decreased, but this change was indistinguishable from control hearts. There was a significant reduction in PP with increasing concentrations, which was clearly reversible after washout of the inotropic agents. The other effects were at least partially reversible. Note, however, that with IBMX, LVP$_{max}$ did not increase again, and the same holds true for (dP/dt)$_{max}$ after milrinone washout.

When the hearts were exposed to equianesthetic concentrations, both halothane (0.8%) and isoflurane (1.3%) significantly depressed LVP$_{max}$ and (dP/dt)$_{max}$, halothane depressing the latter to a greater extent than isoflurane did. Heart rate was significantly depressed and PP increased slightly but significantly in the hearts exposed to halothane (for mean values and statistical significance of differences, see Table 1). Figure 3 depicts recordings from a typical experiment. The negative inotropic effect of isoflurane developed within a few minutes, and after 20 min a new steady state had developed. Exposure of the heart to milrinone (1 μmol/L and subsequently 10 μmol/L) caused a concentration-dependent increase in (dP/dt)$_{max}$ and, in this particular experiment, only a small increase in LVP$_{max}$.

The results from all experiments with isoflurane and halothane are summarized in Figure 4. In general, the positive inotropic effects of the PDE inhibitors were significantly greater with simultaneous exposure to the anesthetics than without. The maximum effect of IBMX was of comparable size in hearts pretreated with either halothane or isoflurane. Milrinone and amrinone clearly produced a greater increase in (dP/dt)$_{max}$ in the presence of isoflurane than they did in the presence of halothane; in fact, amrinone hardly enhanced (dP/dt)$_{max}$ after halothane exposure. Although LVP$_{max}$ was but little elevated under control conditions and merely declined with time, it increased with all three PDE inhibitors in hearts exposed to halothane and isoflurane. With low concentrations of IBMX (<30 μmol/L), the increase in LVP$_{max}$ was greater after halothane than after isoflurane, whereas milrinone and amrinone produced greater effects after isoflurane (Figure 4). After exposure of the hearts to either anesthetic, the PDE inhibitors accelerated HR to a similar extent as in

Table 1. Effects of Isoflurane (1.3%, vol/vol) and Halothane (0.8%, vol/vol) on the Contractile Performance of Guinea Pig Langendorff-Perfused Heart Preparations

	Control	Isoflurane	Control	Halothane
LVP_{max} (mm Hg)	89 ± 5	62 ± 4[a]	94 ± 5	61 ± 4[a]
$+(dP/dt)_{max}$ (mm Hg/s)	1274 ± 61	905 ± 67[a]	1252 ± 64	671 ± 51[a,b]
HR (beats/min)	167 ± 4	155 ± 6[a]	159 ± 6	152 ± 8[a]
PP (mm Hg)	38 ± 2	38 ± 2	39 ± 2	44 ± 2[a,b]

Values are expressed as mean ± SEM of pooled data, i.e., $n = 16$ and $n = 17$ in the halothane and the isoflurane group, respectively; the control values in the two groups are not significantly different from each other. Values for isoflurane and halothane were obtained after 20 min of exposure.

LVP_{max}, maximal left ventricular pressure; $+(dP/dt)_{max}$, maximal rate of pressure development; HR, spontaneous heart rate; PP, perfusion pressure.

[a] $P < 0.05$, isoflurane or halothane compared with their control value by t-test for paired data.

[b] $P < 0.05$, isoflurane compared with halothane, by t-test for grouped data.

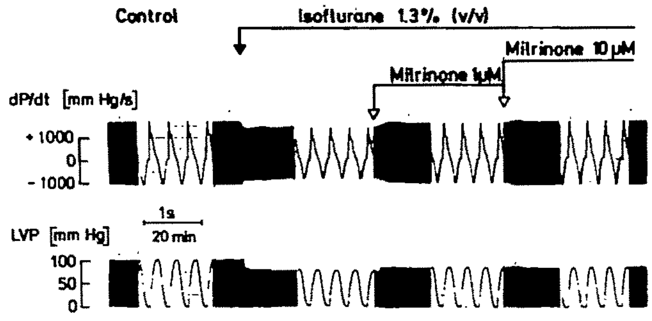

Figure 3. Tracings of LVP and its derivative dP/dt from a typical experiment with isoflurane and milrinone. At the end of the control period, the perfusion medium was switched from carbogen-equilibrated to carbogen plus isoflurane-equilibrated Tyrode's solution for the further duration of the experiment. Milrinone (1 and 10 µM) was added to the perfusion solution in a cumulative manner after the effect of isoflurane had reached a steady state. Time scale: 1 s and 20 min for recordings at fast and at slow chart speed, respectively.

control hearts, with the exception of amrinone, the positive chronotropic effect of which was practically abolished in the presence of halothane. Exposure to halothane and isoflurane had no additional effect on the PDE inhibitor-induced decrease in PP (data not shown).

The results demonstrate that the chronotropic and inotropic changes induced by the PDE inhibitors do not occur in a fixed proportion. In Figure 5, we have plotted the positive inotropic effects produced by the three PDE inhibitors in the absence and presence of the volatile anesthetics against the concomitant changes in HR. In comparison to control conditions, IBMX produced greater increases in contractile performance for a given HR acceleration in the presence of the anesthetics. With milrinone, the situation was similar, although the overall effects were smaller. With amrinone, exposure to the anesthetics greatly reduced the positive chronotropic effects; a clear positive inotropic effect of a similar magnitude as with milrinone, however, was observed only in the presence of isoflurane.

Discussion

Effects of IBMX, Milrinone, and Amrinone in Guinea Pig Hearts

In isolated perfused control hearts, the three PDE inhibitors amrinone, milrinone, and IBMX are able to enhance contractile performance. The positive inotropic effects of PDE inhibitors are accompanied by positive chronotropic actions, and both effects are thought to be related to the elevation of the cellular cyclic adenosine monophosphate content (5). Within the concentration range studied, the maximum increases in HR as well as in $(dP/dt)_{max}$ were different (order of efficacy: IBMX > milrinone > amrinone). It must be mentioned, however, that under different experimental conditions milrinone may increase HR to a greater extent than IBMX does (6).

The order of positive inotropic efficacy was the same as for the chronotropic effect: IBMX > milrinone > amrinone (see Figure 2). With milrinone and amrinone, the changes in $(dP/dt)_{max}$ were biphasic, i.e., with high concentrations, contractile performance decreased again. Because this decline was similar to that seen in time-matched control hearts it is concluded that the positive inotropic effect ceased to develop at high HRs. Incidentally, in hearts paced at high frequencies (280 beats/min), milrinone also no longer enhanced contractile performance (6).

Higher frequencies per se are expected to augment force of contraction (7), but we did not find a strict correlation between positive chronotropic and inotropic effects. For example, with milrinone and amrinone, HR continued to increase in the high concentration range, while contractile performance declined again.

Marked increases in HR with little positive inotropic effect have been described for milrinone and amrinone (8), but milrinone has also been reported to have pronounced positive inotropic effects with little increase in HR (9). In a comparative study of the chronotropic effect in guinea pig right atria and of the positive inotropic effect in papillary muscles, selective

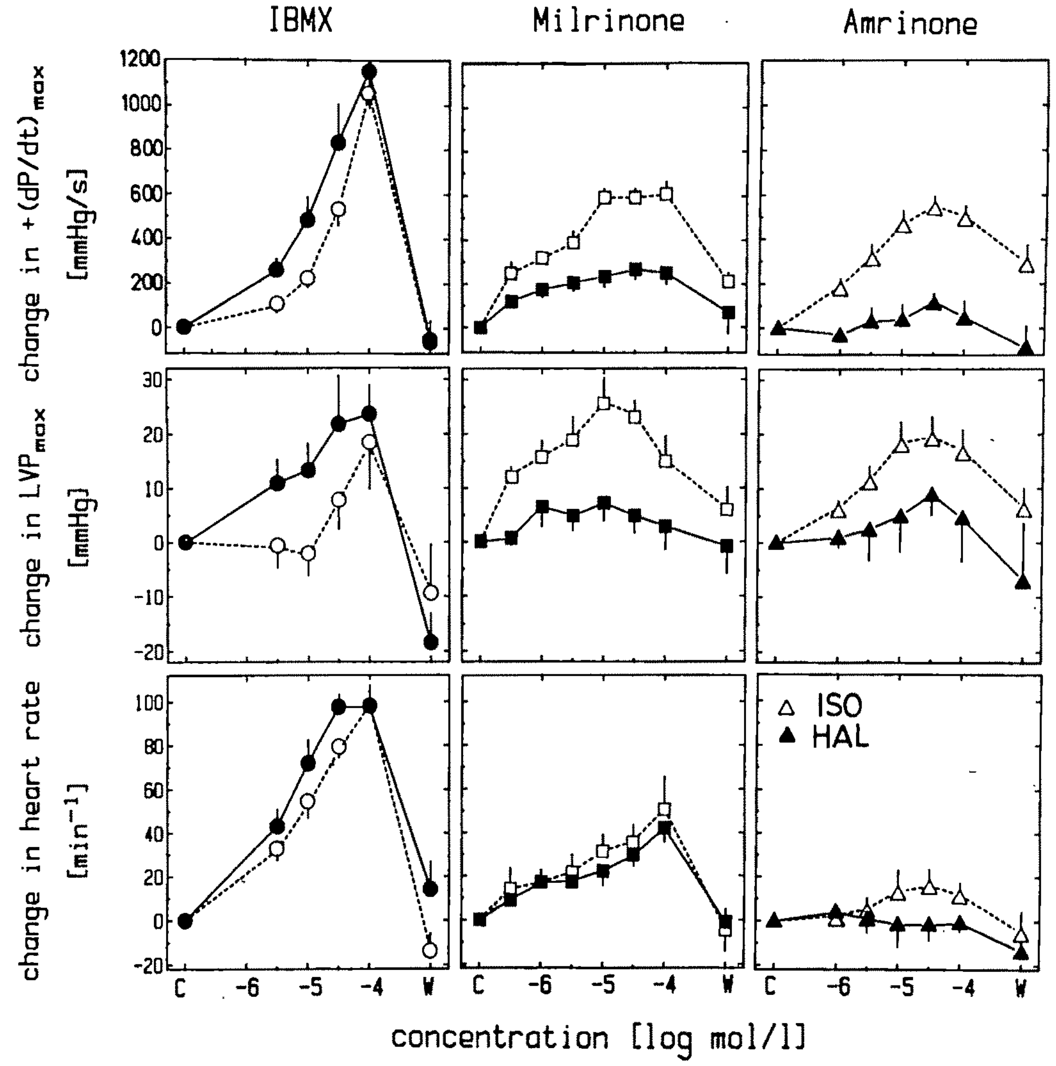

Figure 4. Concentration-response curves for the effects of IBMX (*left column*), milrinone (*middle column*), and amrinone (*right column*) in the presence of halothane (0.8%, vol/vol; *filled symbols*) or isoflurane (1.3%, vol/vol; *open symbols*). The parameters depicted are the change in $+(dP/dt)_{max}$ in mm Hg/s (*upper row*), the change in LVP_{max} in mm Hg (*middle row*), and the change in spontaneous HR in beats/min (*lower row*). Abscissas: concentration of PDE inhibitor in log units (mol/L); C and W indicate values obtained before addition and after washout of PDE inhibitor, respectively. Mean values ± SEM from five to seven hearts. At the following concentrations of the PDE inhibitors (−log mol/L) the differences in values between halothane and isoflurane were statistically significant (two-sided Student's *t*-test for grouped data, $P < 0.05$): for $+(dP/dt)_{max}$: IBMX 5.5, 5; milrinone 6, 5.5, 5, 4.5, 4; amrinone 6, 5.5, 5, 4.5, 4; for LVP_{max}: IBMX 5; milrinone 6.5, 5.5, 5, 4.5; amrinone 6; for HR: IBMX 4.5. All other differences between groups did not reach the level of statistical significance.

PDE III inhibitors (e.g., milrinone) had fewer chronotropic effects than did unselective ones like IBMX; the reason for this is not known (10). Thus, further experiments are required to elucidate the relation between these two actions of PDE inhibitors.

Effects of IBMX, Milrinone, and Amrinone in Hearts Exposed to the Volatile Anesthetics

After exposure to halothane and isoflurane, all three PDE inhibitors still produced their chronotropic and inotropic effects, with the exception of amrinone in the presence of halothane. There were, however, interesting differences in the effects of the PDE inhibitors. The IBMX-induced increase in $(dP/dt)_{max}$ was almost twice as great after exposure to isoflurane or halothane than in control hearts, yet the accompanying increase in HR was similar to that seen in controls. 3-Isobutyl-1-methylxanthine induced maximum increases in $(dP/dt)_{max}$, LVP_{max}, and HR that were similar in the presence of halothane or isoflurane. Milrinone and amrinone, which had little positive inotropic effect in control hearts, were much more effective both in absolute and relative terms in the

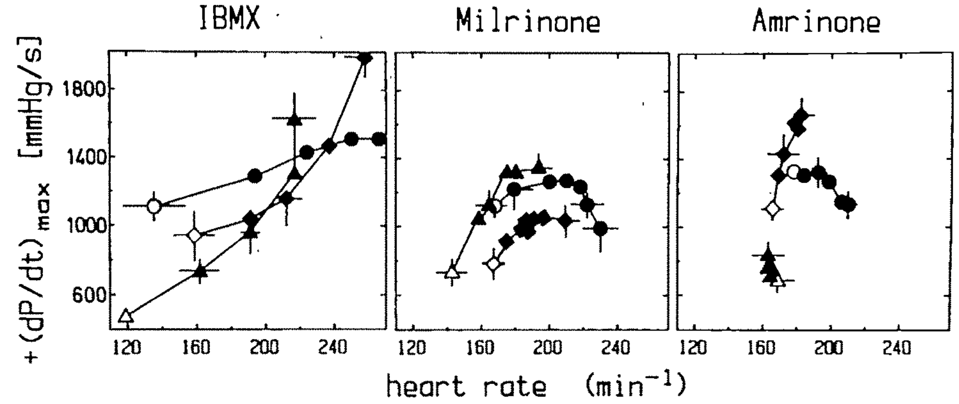

Figure 5. Relationship between the inotropic effect [expressed as $+(dP/dt)_{max}$] and the chronotropic effect (spontaneous HR) for the PDE inhibitors IBMX, milrinone, and amrinone. The guinea pig Langendorff-perfused hearts were perfused with Tyrode's solution equilibrated with carbogen (*circles*), or carbogen plus isoflurane (*diamonds*), or carbogen plus halothane (*triangles*). *Open symbols* indicate values obtained before exposure to PDE inhibitors. Mean values ± SEM of five to seven experiments.

hearts exposed to isoflurane. In halothane-pretreated hearts the drug effects were comparable to those in the controls. The frequency changes caused by amrinone and milrinone, however, were less than in control hearts.

In the presence of halothane, amrinone had a small positive inotropic effect, an effect accompanied by a decrease in HR. The most likely explanation for this finding is that the anesthetics and the PDE inhibitors have opposite effects on the pacemaker mechanism. Indeed, halothane and isoflurane have been shown previously to *decrease* the rate of the sinus node of guinea pig hearts (11) and of beating heart cells in culture (12).

Isoflurane and halothane produce their negative inotropic effect by interference with the contractile cycle at various cellular levels: they inhibit Ca^{2+} influx into the cells (11,13), reduce the uptake and release of Ca^{2+} into the sarcoplasmic reticulum (14,15), and decrease the calcium sensitivity of the contractile proteins (16). Equianesthetic concentrations of isoflurane and halothane depress force of contraction to a similar degree in nonpotentiated isolated cardiac muscle, but isoflurane is less cardiodepressive than halothane in potentiated muscles, especially at high stimulation frequencies (1,2). Although we used equianesthetic concentrations of the volatile anesthetics in our experiments, $(dP/dt)_{max}$ decreased more with halothane than with isoflurane (see Table 1). The high beating rate of 2.5 Hz of the Langendorff-perfused hearts could, therefore, explain the difference in negative inotropic action of the two anesthetics found in our experiments.

The decrease in PP that we observed with the PDE inhibitors is due to the well-known vasodilatory effect of these drugs (6,17), the mechanism of which is as yet not completely understood (18). The volatile anesthetics did not influence this effect, although halothane slightly increased PP (see Table 1 of Reference 19).

In summary, compared with control conditions, PDE inhibitors augmented contractile performance to a greater extent after exposure to volatile anesthetics; the accompanying increase in HR, however, was similar or even smaller. Amrinone and milrinone were more effective in the presence of isoflurane than in the presence of halothane.

The authors gratefully acknowledge the excellent technical assistance of Iris Manthey and Doris Petermeyer. Furthermore they wish to thank Winthrop GmbH for the generous gift of milrinone.

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Recovery of Pancuronium From Peritoneal Dialysate in a Severely Burned Child

Charles W. Hogue, Jr, MD, Jeevendra Martyn, MD, Timothy R. Baker, BS,
and Paul Vouros, PhD

Department of Anesthesiology, Harvard Medical School; Anesthesia Services of the Massachusetts General Hospital
and Shriners Burns Institute; Barnett Institute, Department of Chemistry, Northeastern University,
Boston, Massachusetts

Pancuronium and its metabolites are eliminated primarily by the kidney (1,2). Thus, prolonged neuromuscular blockade may occur if pancuronium is given to patients with altered renal function. Peritoneal dialysis (PD) is often used in patients with renal failure to assist in the elimination of metabolic degradation products. Although many drugs are known to be removed from the body by PD (3), the elimination of pancuronium by this means has not been evaluated, although gallamine is known to be excreted into the peritoneal dialysate (4). In this case report we document the ability of PD to eliminate pancuronium.

Case Report

A previously healthy 3-yr-old 14-kg boy was transferred to the Shriners Burns Institute after suffering an 80% body surface area burn. Poor arterial oxygenation required tracheal intubation and mechanical ventilation of the lungs. Within the first 24 h of admission several episodes of bradycardia and hypotension developed requiring treatment with atropine, epinephrine, and, on one occasion, chest compression. On postburn day (PBD) 4 the blood urea nitrogen was 36 mg/dL and the serum creatinine 2.4 mg/dL (blood urea nitrogen and creatinine were 10 and 0.7 mg/dL, respectively, on admission). Peritoneal dialysis was therefore started both to manage renal insufficiency and to assist in the removal of excess fluid associated with ongoing resuscitation. Each episode of dialysis consisted of 300–400 mL of dialysate infused into the peritoneum for a 2-h equilibration interval.

During his hospitalization the patient received multiple general anesthetics for excision and grafting procedures. It is of note in the present context that he received pancuronium intraoperatively on several occasions (see Table 1). Because of burns to the extremities, muscle relaxant-induced neuromuscular paralysis was not monitored in the perioperative period. The patient was, however, able to open his eyes multiple times in the intensive care unit. The patient's renal insufficiency stabilized with creatinine ranging from 2.7 to 3.0 mg/dL. Fluid balance was consistently positive during the acute phase of his hospitalization, requiring continued PD. Eventually his renal function improved and his clinical condition stabilized, allowing PD to be discontinued on PBD 16. Despite a hospital course that included two cardiac arrests, sepsis, respiratory failure, and multiple episodes of hypotension necessitating the use of vasoactive drugs, the patient's trachea was extubated on PBD 31. He was discharged after an additional month of hospitalization.

After receiving approval from our institutional committee on human studies and after obtaining informed consent from the patient's parents, daily samples of blood, urine, and peritoneal dialysate were obtained between PBD 10 and 16 to measure pancuronium concentrations by mass spectrometry. The pancuronium concentrations are shown in Table 1. The initial plasma concentration of 120 ng/mL on PBD 10 reflects doses of pancuronium given at least 3 days before sampling, particularly the 33 mg (approximately 2.2 mg/kg) given on PBD 7. The peak plasma level of 380 ng/mL occurred after 4 mg of pancuronium was given intraoperatively on PBD 13. Although 10 mg of pancuronium was given on PBD 16, blood sampling postoperatively showed lower pancuronium concentrations than on PBD 14 (4 mg pancuronium given). This discrepancy may be due to the improvements in renal function during this period. The urine sampling was stopped before the

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Accepted for publication February 20, 1991.

Address correspondence to Dr. Hogue. Department of Anesthesiology, Washington University School of Medicine, 660 South Euclid, Box 8054, St. Louis, MO 63110.

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0003-2999/91/$3.50

Table 1. Pancuronium Administration and Elimination[a]

	Postburn day									
	7	8	9	10	11	12	13	14	15	16
Pancuronium given (mg)	33						4			10
Plasma pancuronium concentration (ng/mL)				120	150	185	380	140	160	81
Urine pancuronium concentration (ng/mL)				1330	250	128	95	2200	1700	130
Urine volume (mL)				138	278	278	303	280	384	675
Dialysate concentration (ng/mL)					280	149	58	167	320	140
Dialysate volume (mL)					3400	2850	1400	2174	5500	500
Urinary excretion of pancuronium (mg)				0.18	0.07	0.04	0.03	0.62	0.65	0.09
Dialysate excretion of pancuronium (mg)					0.95	0.43	0.08	0.36	1.76	0.07

[a]Columns represent a 24-h period.

intraoperative administration of 10 mg of pancuronium on PBD 16.

The 24-h urinary and peritoneal dialysate volumes and the concentrations of pancuronium concentrations in these fluids are shown in Table 1. Although the pancuronium concentrations (ng/mL) in urine at times were seven times higher than those in the dialysate, the total amount of pancuronium eliminated by dialysis per 24-h period was consistently higher than that excreted per day by the renal route. During the sampling period the total pancuronium eliminated by the renal route was 1.7 mg whereas the amount excreted through the dialysate was 3.6 mg.

Discussion

The elimination of a drug by PD is influenced by physical and pharmacologic characteristics of the compound including molecular weight, charge, lipid solubility, volume of distribution (Vd), and protein binding (3). Only free drug in the central compartment is available to traverse the peritoneal membrane. That is, only drug in the plasma perfusing the peritoneal membrane is capable of following its concentration gradient into the dialysate. Therefore, drugs like digoxin, with a Vd of 700 L (5), are poorly removed by PD compared with tobramycin, the Vd of which is 16 L (3). The large Vd of digoxin provides a reservoir that may return the drug to a central compartment, limiting the effectiveness of elimination by PD. In contrast, a drug such as ceftriaxone, despite a Vd of 15 L, is poorly dialyzed because it is 90% protein-bound (3). Pancuronium, because of a Vd essentially equal to the volume of extracellular fluid and associated with limited protein binding (6–8), would appear to be easily removed by dialysis. Our results (Table 1) demonstrate that pancuronium is recovered in peritoneal dialysate but only in small quantities. Despite dialysate concentrations (ng/mL) that were usually lower than urine concentrations in our patient, the total amount of pancuronium excreted per 24-h period by PD was consistently higher than that excreted by the dysfunctional renal route. The wide fluctuations in PD pancuronium concentrations (e.g., PBD 13) can be explained by incomplete emptying of dialysate possibly owing to pockets within the peritoneum. The lower concentrations of pancuronium in the dialysate can be explained by dilutional effects of the large volume of dialysate used for PD.

Other factors that may influence the elimination of a drug by PD include characteristics of the peritoneal membrane, blood flow to the peritoneum, dialysate volume, equilibration interval, and competing routes of elimination (3). Blood flow to the peritoneal membrane could potentially be influenced by vasoconstricting drugs such as the epinephrine required in our patient's multiple resuscitations. Competing routes of elimination may be particularly important in burn patients with their characteristically increased extrarenal losses of drugs (9–11). These extrarenal routes of drug loss include leaching of the drug through burn wounds and increased hepatic elimination because of altered hepatic blood flow and hepatic drug metabolizing enzyme activity.

The effective removal of steroidal muscle relaxants such as pancuronium by dialysis may, however, be limited by factors other than the movement across either artificial dialysis membranes or the peritoneum. Vandenbroom and Wierda have documented the elimination of pancuronium and its pharmacologically active 3-desacetyl metabolites through continuous hemofiltration in a patient with renal failure (12). These authors were able to collect only 19 mg of pancuronium in the hemofiltrate from an adult given 105 mg over a 4-day period. Segredo et al. have examined the removal of a metabolite of another steroidal muscle relaxant, vecuronium, by hemodialysis in two critically ill patients receiving a prolonged infusion of the muscle relaxant (13). Although the plasma levels of 3-desacetyl vecuronium decreased after hemodialysis in this latter report, plasma concentrations of this active metabolite of vecuronium increased in the postdialysis period, despite the lack of drug administration. A storage compartment of vecuronium was suggested to release accumulated drug into a central compartment for elimination (13). In their report, Vandenbroom and Wierda measured pancuronium concentrations in various organs removed at autopsy (12). Pancuronium and metabolites could be found in liver, spleen, and other organs. The authors speculate that the high affinity of pancuronium for mucopolysaccharides and chondroitin sulfate found in connective tissue may also cause the drug to accumulate in these tissues (12). Our data for pancuronium (Table 1) support the presence of a storage compartment releasing pancuronium into the plasma. Despite the fact that no drug was administered between PBD 10 and 12 and between PBD 14 and 15, the plasma concentrations of pancuronium continued to increase (Table 1). Unlike these previous reports where the patient received pancuronium or vecuronium over an extended period, our patient received only three doses of pancuronium over a 10-day interval. The large doses administered plus the presence of renal insufficiency allowed for accumulation of pancuronium. Thus, it appears that pharmacokinetic data for pancuronium and vecuronium obtained after shorter periods of study cannot be extrapolated to our clinical situation of altered elimination or to situations of prolonged drug administration.

Original pancuronium assays used fluorometric techniques that failed to distinguish pancuronium metabolites from parent compound (13,14). The mass spectrometric assay used to measure pancuronium concentrations in this report has recently been described (15,16). The lower limit of sensitivity is less than 5 ng/dL with a relative error of 24% at the lowest concentration. Our assay distinguishes parent compound from metabolites. The pancuronium concentrations indicated in Table 1, therefore, reflect concentrations of the parent drug.

Burned patients recover from neuromuscular blockade at plasma concentrations of muscle relaxants that would cause complete paralysis in unburned individuals (17). Agoston et al. (18) have previously shown that recovery of pancuronium paralysis occurs in adults at plasma concentrations of 170 ng/mL. The highest concentration recorded in our patient was 380 ng/mL. Although neuromuscular recovery was not monitored in our patient because of the extent of the burns, our patient was able to open and close his eyes in the intensive care unit, corroborating that burned patients recover from paralysis at higher plasma levels of muscle relaxants (17). As mentioned previously, the continued increase of plasma pancuronium concentrations to levels of 120–185 ng/mL occurred between PBD 10 and 12 and between 14 and 15 despite the fact that no drug was administered to the patient during these intervals. It is possible that patients who are not tolerant to nondepolarizing muscle relaxants could have potentially experienced muscle weakness at these plasma pancuronium concentrations.

In conclusion, this report documents that pancuronium can be eliminated by PD in a severely burned child. However, of a total of 47 mg of pancuronium administered only 3.6 mg of parent drug could be accounted for by PD. The limited effectiveness of PD to remove pancuronium may be secondary to accumulation of drug in one or more storage compartments.

The authors thank Michael Oliveri and the nurses of the Shriners Burns Institute for their assistance in collecting samples for this report.

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Bronchospasm After Intramuscular 15-Methyl Prostaglandin $F_{2\alpha}$ and Endotracheal Intubation in a Nonasthmatic Patient

Daniel M. Cooley, MD, Beth Glosten, MD, J. Romaine Roberts, MD,
Pamela D. Eppes, CRNA, and Randall B. Barnes, MD

Department of Anesthesia and Critical Care, and the Department of Obstetrics and Gynecology, The University of Chicago, Chicago, Illinois

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An analogue of prostaglandin $F_{2\alpha}$, 15-methyl prostaglandin $F_{2\alpha}$-tromethamine (15-M $PGF_{2\alpha}$) (Prostin 15/M, Upjohn Co., Kalamazoo, Mich.) is useful in the treatment of postpartum hemorrhage secondary to uterine atony (1) and in inducing abortion (2,3). Common side effects include nausea, vomiting, diarrhea, and fever. Bronchoconstriction has been reported after exposure to 15-M $PGF_{2\alpha}$ but is rarely clinically important except in asthmatic patients (2–5). We present a case of severe bronchospasm after tracheal intubation in a nonasthmatic patient who had received intramuscular 15-M $PGF_{2\alpha}$.

Case Report

A 32-yr-old gravida 5, para 2 woman was transferred to our hospital 2 h after an elective abortion that resulted in persistent vaginal bleeding. Uterine curettage performed at the transferring clinic failed to control the bleeding, and an intravenous infusion of lactated Ringer's solution with 20 U of oxytocin per liter was started. The only other medication she had received was 10 mg of diazepam orally before the abortion. In our emergency room, physical examination revealed an alert woman with a blood pressure of 90/70 mm Hg and heart rate of 103 beats/min with postural changes. She had mild abdominal discomfort to palpation without signs of peritoneal irritation. Bright red bleeding was present vaginally. Because initial hemoglobin was 6.3 g/dL, a transfusion of 1 U of uncrossmatched type O negative blood was started. She received 0.2 mg of ergonovine maleate (Ergotrate Eli Lilly & Co., Indianapolis, Ind.) intramuscularly.

The patient denied any significant medical history including asthma, smoking, recent respiratory illness, or other pulmonary diseases. She had no history of prior anesthetic exposure. She had no known allergies and was not taking any medications.

The patient was taken immediately to the operating room for a second uterine curettage under monitored anesthesia care. Monitors included electrocardiogram, blood pressure cuff, chest stethoscope, and pulse oximetry. Verbal communication with the patient was maintained throughout the procedure, and nasal prongs were used to give supplemental oxygen. Her blood pressure increased from 85/40 mm Hg initially to 110/60 mm Hg after infusion of 2 U of typed and crossmatched packed red blood cells. She received 50 μg of fentanyl intravenously for sedation and analgesia during uterine curettage. For continued vaginal bleeding, she was given three 250-μg doses of 15-M $PGF_{2\alpha}$ intramuscularly 10, 20, and 40 min after the start of the uterine curettage. Except for three episodes of emesis, the patient tolerated the procedure well. Breath sounds by chest stethoscope were clear, and oxygen saturation was 96%–100%.

Uterine curettage did not reveal any retained products of conception. Uterine perforation was considered a possible cause of the persistent vaginal bleeding, and a laparotomy was planned. Thirty minutes after the third dose of 15-M $PGF_{2\alpha}$, the patient's blood pressure was 110/60 mm Hg and her heart rate was 114 beats/min. General anesthesia was induced by rapid sequence using cricoid pressure and 200 mg of thiamylal followed by 100 mg of succinylcholine intravenously for placement of a 7.0-mm oral endotracheal tube under direct vision of her vocal cords. However, attempts to ventilate her lungs manually required high airway pressures and breath sounds could not be heard. Cricoid pressure was maintained and oxygen saturation remained above 97%. The endotracheal tube was removed and a second 7.0-mm oral endotracheal tube was placed. Peak airway pressures reached 60 cm H_2O, but faint breath sounds were heard with wheezing bilaterally. End-tidal carbon dioxide tension was

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Accepted for publication February 20, 1991.

Address correspondence to Dr. Glosten, Department of Anesthesia and Critical Care, Box 428, The University of Chicago Hospitals and Clinics, 5841 South Maryland Avenue, Chicago, IL 60637.

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0003-2999/91/$3.50

55–60 mm Hg by capnography, and the slope of the alveolar plateau suggested an obstructive process (6). Suctioning of the endotracheal tube was performed easily with no mechanical obstruction or secretions present. Metaproterenol (Alupent Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn.) was given through inhaler without changes in wheezing or airway pressure. Oxygen saturation remained at 96%–100% during this period. Enflurane was given in concentrations up to 1.0% as tolerated. The patient's blood pressure ranged from 108/50 to 120/60 mm Hg with heart rate ranging from 110 to 120 beats/min. Pancuronium was given to maintain muscle relaxation.

An arterial catheter was inserted 20 min after the induction of general anesthesia, and an arterial blood sample, obtained while the patient was being mechanically ventilated with 50% O_2, showed pH 7.11, Po_2 149 mm Hg, Pco_2 56 mm Hg, bicarbonate 17 mEq/L, and hematocrit 23%. The ventilatory rate was increased, and intravascular volume repletion was continued with additional packed red blood cells and crystalloid solution. Aminophylline (5 mg/kg) was infused over 20 min and then continued at 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$. At the completion of the aminophylline loading dose and 70 min after the third dose of 15-M $PGF_{2\alpha}$, peak airway pressure had decreased to 30 cm H_2O and the wheezing had resolved. The patient was found to have a perforation of the left lateral uterine wall and laceration of the uterine artery, which required a hysterectomy.

By the conclusion of the operation and 2.5 h after the third dose of 15-M $PGF_{2\alpha}$, the peak airway pressure was 27 cm H_2O and an arterial blood sample, obtained while the patient was being ventilated with 60% O_2, showed pH 7.29, Po_2 244 mm Hg, Pco_2 37 mm Hg, and bicarbonate 17 mEq/L. Estimated intraoperative blood loss was 1.5–2 L. Total intravenous input for the procedure was 4700 mL crystalloid and 5 U of packed red blood cells.

After surgery and awake extubation, chest auscultation revealed no wheezing, and an arterial blood sample, obtained while the patient was breathing 40% O_2 by face mask, showed pH 7.40, Po_2 206 mm Hg, Pco_2 31 mm Hg, and bicarbonate 19 mEq/L. A postoperative chest radiograph was unremarkable. The aminophylline infusion was discontinued the morning after surgery, and the remainder of the hospital course was unremarkable and without further bronchospasm. Upon further questioning, the patient revealed that two of her children had been diagnosed as having asthma.

Discussion

Possible causes of bronchospasm in our patient include drug reactions, transfusion reaction, pulmonary aspiration of gastric contents, pulmonary edema, undiagnosed asthma, or stimulation associated with tracheal intubation with inadequate anesthesia. Aspiration and pulmonary edema were unlikely, given her rapid improvement, physical examination, and postoperative chest radiograph. Intravenous fluid and blood administration were appropriate for her preoperative and intraoperative blood loss. Anaphylactoid reaction to the induction drugs was considered. A muscle relaxant (including succinylcholine) would be the most likely causative agent (7,8); however, the most frequently encountered clinical signs of such a reaction (secondary to histamine release) are circulatory collapse (68%) and widespread flush (55%). Bronchospasm also occurs in 23% of cases (8). The absence of both hemodynamic instability and cutaneous flushing during induction of general anesthesia argues against an anaphylactoid reaction as the cause of this patient's bronchospasm. A transfusion reaction was possible, but, again, no other clinical signs, such as fever, hives, erythema, or evidence of hemolysis, were present.

The patient's bronchospasm may have been a result of the stimulation of her airway with inadequate anesthesia (9). The induction dose of thiamylal was small (~3 mg/kg), given the patient's hypovolemic state; and attempts to deepen anesthesia with enflurane were limited by her hypovolemia.

Another possible cause of the dramatic bronchospasm seen in this patient is increased airway reactivity in response to intubation due to the previously administered 15-M $PGF_{2\alpha}$. This drug has been shown to cause clinically significant bronchospasm in asthmatic patients (2–4). Mathé et al. found asthmatic patients to be 8000 times more sensitive to the bronchoconstrictive effect of $PGF_{2\alpha}$ than normal patients (4). Both Fishburne et al. (3) and Weir et al. (5) found that $PGF_{2\alpha}$ caused a clinically insignificant increase in airway resistance in normal subjects. The greatest changes in maximum expiratory flow-volume curves occurred between 20 and 60 min after intramuscular injection of $PGF_{2\alpha}$ and these changes persisted for more than 1 h (5).

Our patient tolerated three 250-μg doses of 15-M $PGF_{2\alpha}$ when she was awake without symptoms. The onset of her bronchospasm with intubation and its prolonged duration suggest that the combination of 15-M $PGF_{2\alpha}$ and airway manipulation may have precipitated the bronchospasm. The time-course of our patient's bronchospasm was similar to that reported for pulmonary changes in nonasthmatic volunteers after intramuscular injection (5). She had bronchospasm precipitated by intubation 30 min after her third dose of 15-M $PGF_{2\alpha}$. The bronchospasm lasted 40 min and resolved only after completion of the aminophylline loading dose. This time also coincides with the expected metabolism of 15-M $PGF_{2\alpha}$. Also of interest is this patient's positive family history of asthma. Whether a family history of asthma predisposes patients to bronchospasm after 15-M $PGF_{2\alpha}$ deserves further study.

In summary, a case is presented of severe intraoperative bronchospasm in a nonasthmatic patient that in all likelihood was caused by intramuscular administration of 15-M $PGF_{2\alpha}$ followed by endotracheal intubation. Whether the combination of 15-M $PGF_{2\alpha}$ and endotracheal intubation may commonly provoke bronchospasm in patients not known to be at risk for development of bronchospasm requires further evaluation.

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Anterior Spinal Artery Syndrome After Epidural Anesthesia in a Pregnant Diabetic Patient With Scleredema

Douglas W. Eastwood, MD

Department of Anesthesiology, Case Western Reserve University, University Hospitals of Cleveland, Cleveland, Ohio

This is a report of a patient with diabetic scleredema in whom anterior spinal artery syndrome developed as a complication of an epidural anesthetic. The patient has been followed up for 13 yr since this event in 1977.

Case Report

History from the patient and the hospital record indicated a 19-yr-old, gravida 1, para 0 woman in her 33rd week of pregnancy admitted because of childhood-onset, poorly controlled diabetes mellitus and hypertension. Because of fetal bradycardia not associated with uterine contractions, several hypoglycemic episodes, possible preeclampsia (evidenced by proteinurea, hypertension, and tight puffy skin), and a cervix unfavorable for induction of labor, she was scheduled for cesarean section. Her arterial pressure varied between 120/70 and 140/100 mm Hg. NPH insulin (45 U) was administered daily and blood glucose levels varied from 40 to 550 mg/dL. A hematocrit of 36% was recorded and other laboratory values were normal. Physical examination was compatible with a 33-wk pregnancy. After sedation and topical anesthesia, a one-finger vaginal examination had been accomplished with difficulty because of a tight, painful entroitus. Tight skin, which the patient stated had been present for more than 2 yr, was also noted over the shoulders, arms, thighs, abdomen, and fingers.

After infusion of a liter of lactated Ringer's solution, the patient was seated, the skin prepared, and the epidural anesthetic initiated. Because of chronic pain and stiffness in her upper back, she was unable to flex her chin on her chest. The skin of her shoulders and upper back felt thick and brawny. Insertion of the 17-gauge Tuohy needle through the skin required firm pressure. The epidural space was identified using a fluid-filled syringe for the loss of resistance technique. After placement of 15 mL of 3% chloroprocaine in 2-mL increments, the patient complained of aching discomfort in the back and both legs. No additional volume was added and the ache promptly subsided. The epidural catheter was inserted without difficulty. After supine positioning with lateral uterine displacement, the sensory anesthesia level was T-10. Four additional 5-mL increments of chloroprocaine were required through the catheter to a total of 35 mL to obtain a satisfactory level of anesthesia at T-6. The arterial pressure remained between 140/85 and 105/65 mm Hg throughout surgery and the postpartum period without vasopressor support. Throughout the operation oxygen was administered through a nasal cannula. As the abdominal subcutaneous tissue was incised it remained formed, turgid, and firm to the touch. Anesthesia was satisfactory without supplementation and a 1250-g female infant with Apgar scores of 8/9 was delivered. For postoperative pain relief, three 5-mL increments of 0.75% epidural bupivacaine were added over a 60-min period. The epidural catheter was removed intact.

Postpartum the patient continued to be pain free for 4 h at which time she complained of abdominal discomfort and received intramuscular meperidine. Twelve hours after the end of the procedure, the patient had not recovered all motor power of the lower extremities, she was able to abduct her legs and flex the quadriceps muscles bilaterally, and pinprick sensation was present down to the midthigh and on the perineum. Touch and position senses were present over all areas including the perineum. Sphincter tone was present on rectal examination. Neurology and neurosurgery consultations were obtained. Lumbar puncture was attempted to obtain cerebrospinal fluid for blood and local anesthetic analysis but was unsuccessful. Epidural hematoma was considered but thought to be unlikely and the diagnosis of anterior spinal artery syndrome was made.

Lumbar myelography was attempted but was unsuccessful. A cervical (C1-2) myelogram with iophendylate (Pantopaque) visualized the cervical spinal cord well, the upper thoracic cord poorly, and showed no filling of the lower thoracic or lumbar

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Accepted for publication February 22, 1991.

Address correpondence to Dr. Eastwood, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

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0003-2999/91/$3.50

area. Twenty-four-hour films showed thin strands of contrast media as far down as the S-1 level. An epidural venogram performed 5 days later demonstrated a markedly compressed, very scanty venous pattern throughout the thoracic and lumbar epidural space. Thoracolumbar spinal films over a 2-wk period showed no change in the movement of the contrast material. After skin biopsies were performed the dermatology consultants established the diagnosis of diabetic scleredema, the first symptoms of which had been present for more than 2 yr.

Discussion

The patient has been followed up since 1977 with frequent clinic visits and several hospital admissions. She has control of bowel and bladder and is able to stand but not walk. Touch and position senses remain normal with decreased pinprick sensation below the second lumbar dermatome. One additional intrauterine pregnancy was interrupted surgically and a bilateral tubal ligation was performed. Progression of diabetic scleredema is evidenced by diagnoses of hypertension, decreased renal function, diabetic retinopathy, and restrictive pulmonary disease (vital capacity, 66%; and functional residual capacity, 49% of predicted). The patient continues to complain of painful stiff neck and back, tough stiff skin over her hands that restricts movement, and difficulty injecting insulin through the thick skin of her thighs. Her diabetes remains poorly controlled.

Scleredema was reported by Curzio in 1752, by Piffard in 1872, and more completely described by Buschke in 1902 (1). It may develop after an acute infection in patients with poorly controlled diabetes mellitus or without known cause (2). Characteristically, thickening and hardening of the skin develops on the nape of the neck, shoulders, and upper back and can involve the hands, arms, thighs, and legs. The induration is nonpitting and usually symmetrical (3). Rosenbloom has identified associated syndromes in children with diabetes mellitus including stiff hand, Dupuytren's contracture, carpal tunnel, and limited mobility in large spine and shoulder and small finger joints (4).

Microscopic examination of the skin reveals a normal epidermis, whereas the dermis contains thick collagen bundles that are separated by large interfascicular spaces containing glycosaminoglycans that can be demonstrated with Ascian blue stains (1,5). Subcutaneous tissue, periarticular fascia, and connective tissue in any organ system may be affected including heart (6), lung (7), kidney (7), nerves (7), joints (2,5), breasts (8), thyroid (8), parathyroid (9), and tongue (9).

Anterior spinal artery syndrome results from restriction of blood flow to the spinal cord because of arterial obstruction, compression, or hypotension (10,11). Increased cerebrospinal fluid pressure, venous obstruction, and tumor may limit blood flow (10,12). The cause of the restricted blood flow in this patient is postulated to be a collagen-filled epidural space compressing the vascular supply which was further compromised by the added volume of local anesthetic.

In addition to the complication reported here, other anesthetic hazards of diabetic scleredema are decreased pulmonary function, renal insufficiency, difficult intubation because of neck and jaw joint immobility and enlarged tongue, thickened skin increasing venipuncture difficulty, poorly compressible arm tissues leading to erroneously high indirect arterial pressure recordings, and varied absorption of insulin from collagen-filled subcutaneous tissue.

In summary, this is a report of anterior spinal artery syndrome arising as a complication of epidural anesthesia in a patient with diabetic scleredema. It is postulated that the restriction of arterial blood flow to the spinal cord was caused by marked increase in the epidural pressure. The increased pressure was the result of the addition of 35 mL of local anesthetic into an epidural space containing noncompressible collagen which had reduced the volume of displaceable blood and cerebrospinal fluid.

I wish to thank Helmut F. Cascorbi, MD, for review of the manuscript and encouragement in its preparation.

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Epidural Air Associated With Multiradicular Syndrome

Rafael Miguel, MD, Steven Morse, MD, and Reed Murtagh, MD

Departments of Anesthesiology and Radiology, University of South Florida College of Medicine and the H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

Epidural opioids injected through permanently implanted epidural catheters are used increasingly to control intractable pain. Not surprisingly, complications are also occurring with increasing frequency. The epidural space is relatively large at the lumbar level, but becomes markedly smaller cephalad. Therefore, injection of fluid into the thoracic epidural space could cause radicular compression. To the best of our knowledge, this side effect has not been reported previously. We report a case of acute radicular pain caused by initial injection of preservative-free morphine through an epidural catheter placed high in the thoracic spine.

Case Report

The patient, a 64-yr-old, 120-kg man, was admitted to the Cancer Center with adenocarcinoma of the prostate that had metastasized to bone. Prior treatment included prostatectomy, bilateral orchiectomy, interstitial seed implants of ^{125}I, and radiation. Despite therapy, progression of the disease was seen with multiple bony metastases to ribs, thoracic vertebrae, humerus, and hips. Palliative radiation reduced the pain in these areas, except in the cervicothoracic spine and interscapular area.

Upon arrival at the Cancer Center for pain control, the patient was taking 180 mg of long-acting oral morphine (MS-Contin, Purdue-Fredericks, Norwalk, Conn.) every 8 h, with 30 mg of morphine sulfate injected subcutaneously five times daily. On this regimen, the patient was still in severe pain that prevented sleep and interaction with family members. To determine his narcotic requirement, intravenous patient-controlled analgesia was begun and titrated to an average maintenance dose of 22 mg/h, which provided acceptable pain relief.

Attempts to change the medication regimen from an intravenous to an oral route were unsuccessful. With a conservative 2.5:1 oral-to-intravenous conversion ratio, the patient initially responded favorably to 420 mg of oral morphine three times daily, but he soon became obtunded and had periods of apnea. Attempts to reduce the dosage of morphine caused an exacerbation of pain. Consideration was given to the administration of epidural narcotics in an effort to minimize the side effects and to control the pain.

A "bullet-tipped" epidural catheter with side holes (Perifix, Burron, Bethlehem, Pa.) was placed at T-4 using a 17-gauge Tuohy needle, a midline approach, and a loss-of-resistance technique with air. During the procedure, 5 mL of air was injected into the epidural space. The catheter was threaded 3–4 cm cephalad. A weak local anesthetic injection was used epidurally to avoid respiratory impairment and to document correct placement of the catheter tip. Ten milliliters of 0.094% bupivacaine was injected and effected complete abolition of the shoulder and interscapular pain. Dermatomal segment spread in a caudad direction was documented to the sixth thoracic dermatome. Preservative-free morphine sulfate (Astramorph, Astra Laboratories, Westborough, Mass.), 20 mg/20 mL, was injected into the epidural catheter every 8 h. Oral morphine was tapered 50% daily until it was discontinued. The patient's mental status improved continuously. The epidural morphine dosage was increased to 30 mg three times daily to achieve adequate pain relief.

Three days after insertion of the temporary catheter, the patient was taken to the operating room for placement of a permanent epidural catheter (DuPen Catheter, DAVOL, Cranston, R.I.). Using local anesthesia, a midline approach, and a loss-of-resistance technique with air, the catheter was inserted at T-4. Approximately 10 mL of air was utilized in two attempts to identify the epidural space, as some difficulty was encountered in threading the catheter. The catheter was then tunneled and exteriorized at the left inframammary area. Correct placement was documented intraoperatively with fluoroscopy after an injection of 3 mL of nonionic contrast material (Isovue 200, Squibb Diagnostics, New Brunswick, N.J.).

In the postanesthesia care unit, after negative

Accepted for publication February 20, 1991.

Address correspondence to Dr. Miguel, H. Lee Moffitt Cancer Center and Research Institute, P.O. Box 280179, Tampa, FL 33682.

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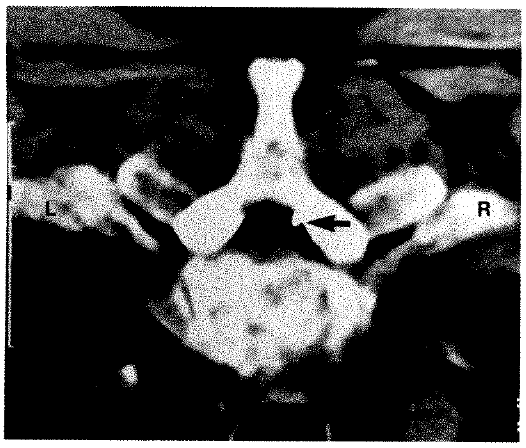

Figure 1. Computed tomography scan at vertebral level T-4 shows catheter in the epidural space (*arrow*). The epidural space is distended with air. Note osseous metastases involving the vertebral body.

aspiration, attempts to inject the 30-mg (1 mg/mL) dose of morphine solution met with sharp, excruciating pain across the left shoulder, chest, and arm. Decreasing the rate of injection did not prevent the pain from reappearing. Injection was discontinued, and the patient was transported to the Radiology Department for documentation of catheter tip location. Using nonionic contrast material, spot radiographs were taken. The catheter tip was visualized in the epidural space at the level of T1-2. Serpiginous and nodular filling defects were seen in the epidural space, and computed tomography was recommended to rule out tumor invasion. Computed tomographs showed a low-absorption image, consistent with gas in the epidural space, dorsal to the dural sac. The catheter was also in the dorsal epidural space. No evidence of tumor extension was seen (Figure 1).

The morphine was concentrated to a 10-mg/mL solution, and the patient received his 30-mg (3 mL) dose without sequelae. The patient recovered and was discharged from the hospital the following day. Eight months later, the catheter was still in place, and the patient was doing well on the same dosage and volume (i.e., 30 mg/3 mL) of epidural morphine.

Discussion

Use of the epidural route of drug administration has dramatically increased in the last 10 yr because of advances in spinal neuropharmacology. Wang's initial study in 1979 established intraspinal narcotics as a potent tool in combating cancer pain (1). We now know that side effects are more commonplace than described by Wang, and we have observed side effects not previously described.

Some of these side effects are related to the technical aspects of epidural catheter insertion and others to the epidural anatomy. Cervical positioning of the catheter tip was effected in this case because the majority of the patient's pain was in the interscapular area. Little or no epidural space exists above C-3 (2). Between C-3 and T-1, the cervical spinous processes become progressively horizontal, thus facilitating access (2,3). With a flexed neck, the lower cervical epidural space will widen to 3–4 mm, from 2 mm at C-3 (2), with marked negative pressure. Caudad, the vertebral canal becomes larger as it descends, contributing to epidural space enlargement. This larger space makes the midthoracic area attractive for epidural access, although the spinous processes are markedly oblique.

Possible causes of pain on epidural injection include direct impingement on a nerve root, irritant components of the solution (e.g., glycol or alcohol), rapid injection, or presence of a space-occupying lesion. In our patient, a preservative-free solution was diluted at the bedside, ruling out the possibility of irritating solutions contributing to the pain. Characteristically, an excessively rapid injection produces a mild discomfort that resolves quickly when the rate of administration is decreased. Our patient experienced pain despite slow injection. Impingement on a nerve root, migration into a dural sleeve, and the presence of a space-occupying lesion were real concerns and prompted the request for radiologic reconfirmation of catheter tip location.

Air injected around nervous tissue may be detected for several days radiographically. Air-trapping in the epidural space has been postulated as an etiologic factor for incomplete block during lumbar epidural anesthesia (4,5). Because the dimensions of the lumbar epidural space are much greater than those at the high thoracic/low cervical area (5,6), no algetic response to injection was elicited in the patients of these studies (4,5). With the assumption of some contact with dura, pain relief should not be affected by air when epidural narcotics are used because their site of action is not in the epidural space (7).

Because alternate causes of pain on injection were excluded, we conclude that pain on injection in this case was caused by radicular compression effected by the accumulated combined volume of air and injectate when the epidural space was accessed twice with air in 3 days. This conclusion was further supported by the lack of pain with a reduced volume of injectate.

The loss-of-resistance technique is the most commonly recommended technique for confirming entry into the epidural space. Whether air or fluid is used is normally left to the practitioner's discretion. Although air may remain in the body, or in this case, the epidural space, for several days, saline is readily absorbed. A stated drawback of saline is dilution of the local anesthetic, which reduces efficacy (4). This hypothesis should not be applicable to epidural narcotics.

A case of air-trapping in the cervicothoracic epidural space causing radicular pain is presented. To eliminate this potential side effect, we recommend limiting the volume of injectate and using saline instead of air in the loss-of-resistance technique in this region.

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Letters to the Editor

Action of Thiopental in Isoniazid-Induced Seizures: GABA Augmentation or Electroencephalographic Suppression?

To the Editor:

Bredemann et al. (1) recently described the effective use of thiopental to control isoniazid-induced seizures in one patient, concluding that thiopental augmented central nervous system (CNS) γ-aminobutyric acid (GABA) activity at the postsynaptic GABA receptor-ionophore complex. In turn, this GABAergic action was thought to oppose the GABA-inhibitory effects of isoniazid. This provides an opportunity to discuss additional factors regarding general anesthetic agents and status epilepticus.

The administration of a single dose of pyridoxine equivalent to the gram amount of ingested isoniazid is well accepted in the treatment of isoniazid-induced seizures (2), although the role of GABA in the development of this form of seizures is not clearly understood. Initial animal studies on the biochemical mechanism involved in isoniazid-induced seizures indicated that low CNS GABA levels were causative (3). However, subsequent animal research has demonstrated a lack of correlation between onset of convulsions and decrease in CNS GABA (4). Furthermore, isoniazid produces an initial decrease in brain GABA followed by a subsequent increase to twice the normal levels (5). These studies further suggest that isoniazid-induced seizures may be more closely related to CNS levels of glutamic acid decarboxylase, the enzyme responsible for the synthesis of GABA (5). This question is further clouded by the clinical practice of neurologists who use isoniazid in various neurologic conditions to increase CNS GABA (6). Therefore, Bredemann's conclusion regarding thiopental, GABA, and isoniazid-induced seizures may be specious. However, if augmentation of CNS GABAergic activity is a specific therapeutic goal in this form of seizures, then a GABA analogue such as baclofen or a GABA precursor such as L-glutamine could be considered.

The use of general anesthetic agents (parenteral and inhalational) in the treatment of status epilepticus has been previously reported. Lowenstein et al. (7) used thiopental, pentobarbital, and methohexital in 14 patients with status epilepticus of various etiologies, while Kofke et al. (8) described the effects of 1–55 h of isoflurane administration in 9 patients with refractory status epilepticus. These reports indicated that the anesthetic agent was uniformly effective in controlling seizure activity. The predominant mode of action of these agents appears to be directly on the electroencephalogram or, as Kofke suggests, "the epileptic neural generator (8)." Both thiopental and isoflurane are noted for their ability to produce electroencephalographic burst suppression and eventual isoelectricity. Kofke et al. (8) recommend an electroencephalographic burst-suppression interval of 15–30 s as a therapeutic goal, which correlates with maximal depression of cerebral metabolism in animals (9).

I commend Bredemann and colleagues for this interesting report, which provides additional confirmation of the therapeutic efficacy of general anesthetic agents in refractory status epilepticus and the importance of the anesthesiologist's intervention when other conservative treatment measures are unsuccessful.

Paul G. Loubser, MB, ChB
The Institute for Rehabilitation and Research
Baylor College of Medicine
Houston, TX 77030

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Complete Airway Obstruction of Armored Endotracheal Tubes

To the Editor:

Because polyvinylchloride endotracheal tubes (ETTs) are susceptible to airway obstruction, especially with the patient's head and neck in certain positions (1), wire-spiral armored ETTs are often used in neurologic and spinal surgery (2–4). We report on two patients in whom airway obstruction nevertheless developed after posterior spine instrumentation in spite of the fact that an armored ETT had been used specifically to avoid such a complication.

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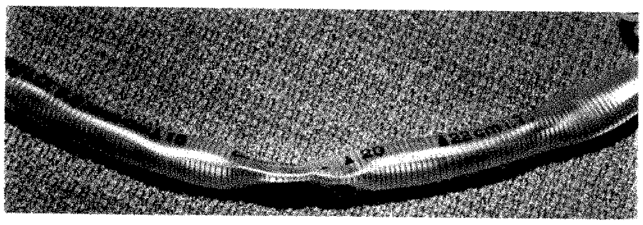

Figure 1. The reinforced ETT from case 1, demonstrating the permanent crush that caused complete airway obstruction.

One patient (case 1) was a 27-yr-old woman who underwent correction of spondylolisthesis and in whom a 7.0-mm-ID wire-spiral reinforced ETT (Malinckrodt Inc., Glens Falls, N.Y.) was used. Sudden complete airway obstruction developed in the patient in the recovery room while her trachea was still intubated. Laryngoscopy showed the ETT to be properly placed but bitten so hard as to be completely and irreversibly obstructed (Figure 1). As soon as the ETT was removed, the obstruction cleared.

The second patient (case 2) was a 16-yr-old girl undergoing spine fusion and instrumentation for idiopathic scoliosis. The patient's trachea was intubated with a 7.0-mm-ID reinforced ETT (Malinckrodt) to prevent kinking. Approximately 20 min after arriving in the recovery room, arterial desaturation and paradoxical respirations developed. The patient was found to be biting the ETT. Insertion of an oral airway as a bite-block did not relieve the obstruction. The wire-reinforced ETT had been irreversibly so compressed that the lumen was obstructed. The reinforced ETT was, therefore, removed and replaced by a polyvinylchloride tube.

These cases emphasize that use of a wire-spiral ETT does not always prevent airway obstruction. Airway obstruction occasionally occurs with an ETT that is not reinforced if the patient bites on the tube during emergence from anesthesia; however, as soon as the jaw relaxes, the obstruction of the ETT is usually at least partially relieved. The reinforced ETTs used in the present two cases retained their crushed shape after biting, permanently distorting the imbedded wire and causing irreversible complete obstruction. Although placement of an oral airway as a bite-block before emergence from anesthesia probably would have prevented this complication, such airways are not always used because of dental problems, abnormal oral anatomy, or the personal preference of the anesthesiologist. A bite-block may well be indicated when armored ETTs are used.

Bruce D. Spiess, MD
Department of Anesthesiology, RN-10
University of Washington
Seattle, WA 98195

David M. Rothenberg, MD
Susan Buckley, MS, CRNA
Department of Anesthesiology
Rush-Presbyterian-St. Luke's Medical Center
Chicago, IL

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Erroneous Measurement With Invasive Monitoring of Blood Pressure

To the Editor:

We would like to call attention to a situation in which it is possible to obtain erroneous measurements when using invasive blood pressure methods. The Sorenson Transpac No. 42587-01 kit from Abbott Critical Care Systems is an invasive blood pressure monitoring system that consists of a transducer and associated fluid tubing. A monitor-specific adaptor cable is used to connect the transducer to the monitor with which it will be used. In particular, we are referring to the Hewlett-Packard Component Monitoring System (Merlin) pressure module (model M1006A).

The Hewlett-Packard Merlin invasive pressure modules are designed so that they can be used with pressure transducers having either the standard sensitivity (output) of $5\ \mu V \cdot mm\ Hg^{-1} \cdot V^{-1}$ (excitation) or the higher nondisposable, quartz transducer sensitivity of $40\ \mu V \cdot mm\ Hg^{-1} \cdot V^{-1}$. The connector socket on the pressure module has provision for 12 pins, which are approximately 1 mm in diameter by 7 mm long. However, the adaptor cable itself has only 7 pins: 2 for excitation, 2 for signal, 1 shield (ground), and pins numbered 5 and 8, which are connected together (shorted). Pin number 8 stands somewhat separated from the other pins, and thus has less protection against damage if the connector is inserted out of alignment with its mating socket in the monitor (see Figure 1).

When the standard sensitivity transducer is used, pins number 5 and 8 must be shorted together by a jumper in

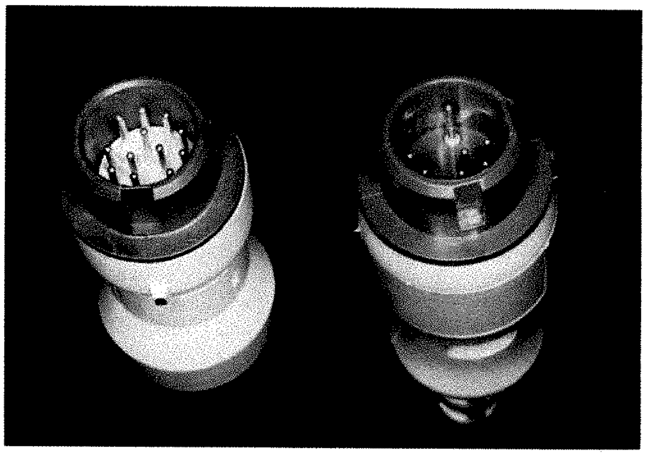

Figure 1. *Left:* old style connector with 12 pins. *Right:* new style connector with 7 pins. (Pin number 8, at risk of breaking off, is in the 12 o'clock position.)

either the transducer or, as was the case here, in the adaptor cable. If pin number 8 breaks off, the short circuit is opened and the monitor responds as though the transducer had the higher sensitivity. Pressure readings that are one-eighth of the actual values will then be reported.

On several occasions, when preparing to monitor arterial pressure, we found adaptor cables in which pin 8 was broken off. This damage was most likely the result of trying to force the connector into its socket when not properly aligned. We were fortunate in that it was arterial pressure being monitored; it was thus relatively easy to recognize erroneous readings. If central venous or pulmonary arterial pressures were being monitored, the patient might have been assumed to be hypovolemic and treated aggressively with fluids, possibly resulting in pulmonary edema.

As far as we know, Hewlett-Packard is the only company that manufactures pressure monitors that are capable of using transducers with either sensitivity. We have discussed this situation with representatives from both Abbott Critical Care Systems and Hewlett-Packard. Some measures that might be taken to prevent this problem from occurring include a sturdier construction of the adaptor cable, or eliminating it completely and having a one-piece cable from the transducer. Better yet, quartz transducers could be modified to conform to the much more prevalent sensitivity standard of 5 $\mu V \cdot mm\ Hg^{-1} \cdot V^{-1}$. As a precaution, a transducer simulator (Sorenson Transpac No. 42601-01) can be used to verify the integrity of the monitor and adaptor cable and to assure that the monitor is working properly with the correct sensitivity.

Since this problem was reported to the Abbott Corp., they have taken another approach. Adaptor cables are now supplied with a full 12 pins to match the monitor socket, instead of only the 7 pins needed for the transducer operation. The additional (operationally inactive) pins provide some support and protection to help prevent the stand-alone pin (number 8) from buckling if the pins are not absolutely aligned in the socket when the cable connector is plugged into the monitor. So far, our experience is that this new cable does prevent the problem from occurring. However, as long as there is provision to use transducers of two sensitivities, the potential exists for this problem to reoccur.

Andres T. Navedo, MD
Alvin Wald, PhD, CCE
Department of Anesthesiology
Columbia-Presbyterian Medical Center
630 West 168th Street
New York, NY 10032

A Potential Hazard Associated With Misunderstanding of Pulse Oximetric Readings

To the Editor:

The case report by Bailey et al. (1) of electrocautery-induced airway fire during tracheostomy illustrates what I believe to be a potential hazard associated with the use of pulse oximetry.

On many occasions I have observed anesthesiologists—particularly those in training—to be dissatisfied with pulse oximeter readings of oxygen saturation (Sp_{O_2}) less than 99% or even 100%. To treat this "problem" the F_{IO_2} is increased. This is clearly not always either necessary or appropriate, especially as large changes in oxygen tension may not be detected if Sp_{O_2} is maintained on the plateau of the oxyhemoglobin dissociation curve.

In the case in question, ventilation with 100% oxygen resulted in a Pa_{O_2} of 323 mm Hg compared with a preoperative value of 83 mm Hg while breathing 40% oxygen. It therefore appears that ventilation with 100% oxygen was not necessary for the entire duration of the anesthesia, although it is always a prudent measure before removal of the tracheal tube and insertion of the tracheostomy tube. The anesthesiologists may have been persuaded to use 100% oxygen because of the low Sp_{O_2} reading, although in the face of the documented Pa_{O_2}, the validity of the Sp_{O_2} reading must have been questioned. With the suspicion of preoperative pneumothorax, nitrous oxide was quite rightly not used, but the patient could have been ventilated safely with an air/oxygen mixture. The fire may then have been avoided.

Although pulse oximetry helps the anesthesiologist to detect episodes of desaturation early (2), it has been difficult to prove that routine use of pulse oximetry reduces morbidity and mortality. We must all be vigilant to ensure it never *contributes* to morbidity and mortality by causing use of unnecessarily high concentrations of oxygen in the inspired air, especially when electrocautery is used in the airway.

Peter C. Stride, FFARCS
Department of Anesthesiology
University of Texas Medical Branch
Galveston, TX 77550-2778

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Transient Anisocoria After Intravenous Administration of Butylscopolamine

To the Editor:

In modern anesthesia, the pupil is less frequently evaluated as a monitor of anesthetic depth than in the era of ether anesthesia. Nevertheless, anisocoria in the unconscious patient is an ominous sign that might suggest central nervous system pathology. I recently experienced a case of anisocoria after intravenous administration of butylscopolamine.

A 70-yr-old man was scheduled for sigmoid colectomy for adenocarcinoma. Anesthesia was induced with 0.2 mg fentanyl and 150 mg thiopental, followed by 100 mg succinylcholine and endotracheal intubation. After intubation, both pupils were 2 mm in diameter. Anesthesia was maintained with 30% oxygen, 70% nitrous oxide, 0.5% enflurane, and continuous infusion of lumbar epidural lidocaine. Eighty-five minutes after the start of operation, 20 mg butylscopolamine was administered to relieve intestinal spasm. Four minutes later, the patient's left pupil had enlarged in comparison with the right pupil. Diameter of the left pupil was 6 mm and that of the right pupil was 2 mm. The mydriatic pupil was unresponsive to light. Although the mechanism of this anisocoria was not clear, it was speculated that butylscopolamine had had some effect on the pupil size judging from the temporary relationship. The anisocoria resolved over the course of the succeeding 60 min without any treatment and the patient showed no neurologic deficit postoperatively.

There are few reports studying the effect of systemic medications on the size of the pupil during general anesthesia (1,2). As butylscopolamine is an anticholinergic, it can theoretically inhibit ciliary ganglion and dilate the pupil. But it is difficult to explain why it might cause anisocoria. I would like to know if anyone is aware of the mechanism or may have had a similar experience.

Shuya Kiyama, MD
Department of Anesthesiology
School of Medicine, Keio University
35 Shinanomachi, Shinjuku-ku
Tokyo 160, Japan

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Another Cause for Obstruction of Intravenous Infusion Tubing

To the Editor:

A 30-yr-old woman was admitted for emergency cesarean section secondary to breech presentation with a prolapsed cord. She arrived in the operating room with an Abbott Y-type blood infusion set with bulb pump (No. 8949) and an in-line three-way stopcock connected to a 16-gauge intravenous catheter inserted in a forearm vein. Rapid sequence induction of general anesthesia was planned because of the emergent nature of the surgery. After appropriate premedication and preoxygenation, 250 mg thiopental was injected via the stopcock followed by 100 mg succinylcholine. Immediately after the injection of succinylcholine, the intravenous fluid stopped infusing. Inspection of the cannulation site, stopcock, and tubing clamps revealed no obvious problem. Induction of anesthesia was achieved with the thiopental; however, no muscle relaxation occurred as the succinylcholine remained in the intravenous tubing. Tracheal intubation was easily performed without muscle relaxation. A second intravenous line was inserted and the remainder of the surgery was uneventful.

Inspection of the nonfunctional infusion set revealed that the distal ball bearing in the bulb pump was displaced above the valve housing, effectively occluding the lumen and preventing outflow (Figure 1). This probably occurred because the succinylcholine was injected with the stopcock incorrectly closed to the patient distally, but open to the infusion set proximally. The back pressure from the injection unseated the ball bearing into the outflow tract. This was subsequently confirmed by repeating the maneuver on identical infusion sets. Furthermore, any distal occlusion resulting in increased back pressure upon injection (i.e., crimping the intravenous line distally rather than proximally) could result in a similar obstruction as minimal force is required to dislodge the ball bearing.

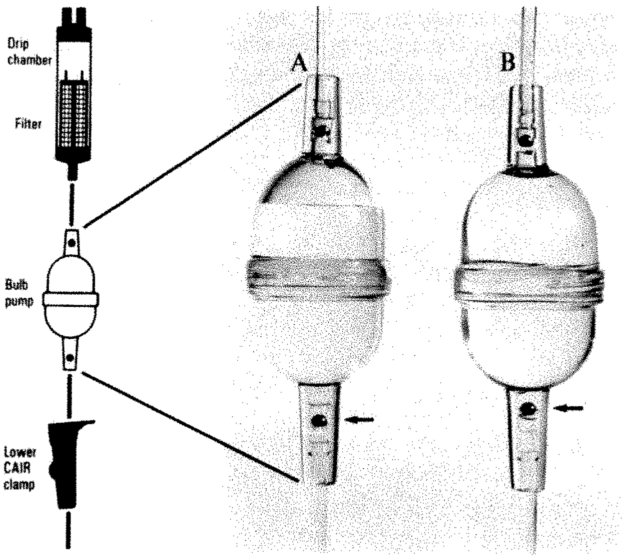

Figure 1. Diagrammatic illustration of infusion set with photographic enlargement of bulb pump. **A.** Valve with ball in proper position (*arrow*). **B.** Valve with ball displaced proximally (*arrow*) causing complete outflow obstruction.

This incident demonstrates that intravenous infusion sets with ball valves similar to the one described are prone to complete occlusion. In view of this potentially serious complication, we suggest avoiding such infusion sets until the bulb pump valve is redesigned.

Howard Bennett, MD
Department of Anesthesia
Evanston Hospital
2650 North Ridge
Evanston, IL 60201

Raymond Glassenberg, MD
Department of Anesthesia
Northwestern University Medical School
Chicago, IL 60611

Of Stethoscopes and Stopcocks

To the Editor:

A simple three-way stopcock can greatly improve the information gleaned from precordial stethoscopes. In the set-up shown (Figure 1), two precordial stethoscopes joined to a three-way stopcock using segments of cut

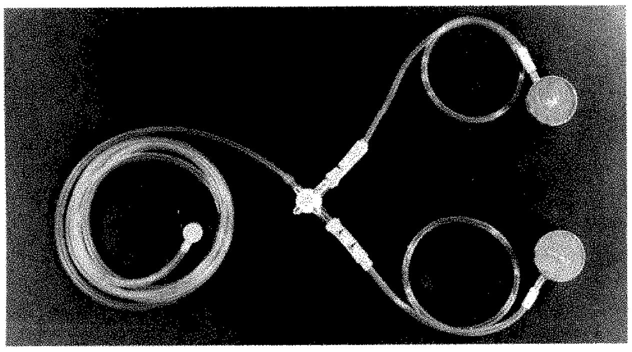

Figure 1. Two precordial stethoscopes attached to a three-way stopcock allowing independent auscultation of each lung. When the stopcock is open to both sides, a parallel input is obtained that amplifies the signal.

endotracheal tubes are attached to an earpiece. By placing these on the left and right sides of the chest, it is possible to monitor breath sounds from both sides by altering the position of the stopcock. This is particularly useful in "field avoidance" situations where detection of one-lung anesthesia may be otherwise difficult.

To overcome the acoustic imperfections of this mode of monitoring, variations on the above theme are possible. One limb can be attached to an esophageal stethoscope, the other to a precordial stethoscope, allowing switching between the two. One often finds that either heart or breath sounds are best heard with one particular type of stethoscope. Finally, leaving the stopcock open to both limbs provides a parallel input that, in effect, amplifies a poor signal. It should be remembered that this mode of monitoring is qualitative and has been relegated to a backup system in the presence of pulse oximetry and capnography (1).

Ed Lee, MB, BCh, FFARCSI
Department of Anesthesiology
Vanderbilt University Medical Center
Nashville, TN 37232

Reference

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Endotracheal Tube Cuff Pressure in the Use of Nitrous Oxide

To the Editor:

We read with interest the letter by Patterson and Keane (1) in which cuff herniation was diagnosed intraoperatively. They used room air to inflate the cuff and then had obviously used a technique using nitrous oxide during the surgical procedure. There was increased distention of the cuff with eventual herniation causing partial occlusion of the tip of the tube. The cause was diffusion of nitrous oxide into the cuff faster than the nitrogen in the air-filled cuff was able to leave.

We performed a series of experiments several years ago (unpublished), and Dr. Ted Stanley has published three articles (2–4), relating to nitrous oxide diffusion into an air-filled endotracheal tube cuff. These experiments readily explained the expansion of the endotracheal tube cuff due to the solubility of nitrous oxide relative to air. Nitrous oxide, it must be remembered, is 34 times more soluble than nitrogen in blood; this phenomenon explains why nitrous oxide should not be used in patients with a pneumothorax, bowel obstruction, or similar conditions. Our experiments, as well as Stanley's, indicate that a similar event takes place across the membrane of the cuffed endotracheal tube.

One approach to solving the problem (5) is to use an elaborate system of equalizing pressures between the cuff, the balloon, and the outside world at, we would suspect, a moderate cost for the equipment. The problem could be obviated, however, if one used the gases to be administered to the patient or 100% nitrous oxide to inflate the cuff of the endotracheal tube. Thus, one would not have to worry about the increased size and consequent pressure in the cuff during the case. Herniation of the cuff due to increased volume would also be obviated.

Carl G. Fischer, MD
Department of Anesthesia
Shrine Burns Institute
202 Goodman Street
Cincinnati, OH 45219

D. Ryan Cook, MD
Department of Anesthesia
Children's Hospital
125 DeSoto Street
Pittsburgh, PA 15213

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Section Editor
Norig Ellison

Book Reviews

Problems in Anesthesia

Chronic Pain Series, Volume 4, No. 4, December 1990
Bradford D. Hare and Perry G. Fine, eds. Philadelphia:
J. B. Lippincott Company, 1990, 690 pp, $30.00 (single issue), $65.00 (annual subscription for four issues).

The preface declares that this text will serve as a concise yet comprehensive guide for the practicing anesthesiologist or anesthesiologist-in-training who has an interest in chronic pain. Looking at it from the editors' intent, the book unfortunately falls way short of the intended call in not only the topics covered but the overall direction that chronic pain seems to be going, at least in anesthesia circles. The book (Volume 4, No. 4; 137 pages in length) certainly starts out well with an introduction to chronic pain where the recommended approaches are outlined with emphasis on the direction of the psychological orientations of Wilbert Fordyce John Bokan. The principles are listed, starting with the notion "there are no chronic pain emergencies." This reviewer would only agree if the pain is not your own pain or the pain of someone you like. The principles are developed with a more psychology-oriented tone than many of the recent anesthesia and more aggressive pain management techniques would indicate.

The chapter on the nociceptive system and persistent pain syndromes is quite good. Possibly the highlight of the book is the chapter on the uses and misuses of medication in the management of chronic non-cancer pain. The chapter is in the form of nicely thought out approaches that indeed would be useful if one needed to sit down and think the medications over. This reviewer particuarly liked the questionnaires and the table at the end of the chapter.

On the other hand, the section on the role of nerve blocks and injections in the management of chronic pain problems is limited in scope and distinctly dangerous. On page 601 the maximum recommended dose for the local anesthestic listed is the same for local, intravenous regional, peripheral nerve block, stellate, lumbar sympathetic block, and epidural, which in the hands of those who do not have sufficient discriminating experience may lead to lethal complications. The technique described for stellate ganglion block also is out of date and hazardous by present-day standards. Furthermore, on page 611, while describing intravenous regional sympathectomy, a nice trick is given for the imaginative use of guanethidine by dissolving a guanethidine tablet in lidocaine; however, no data are given for the effectiveness of such an approach at a time when guanethidine has not been released to the general market by the FDA. Reserpine is mentioned in a negative tone without pointing out to the reader that reserpine is also not available for use.

Apparently for the sake of brevity, neurolytic techniques are mentioned but fail to be described in an adequate and safe manner for those who wish to use such therapeutic modalities when everything else has failed. On the other hand, the references are quite good and the authors may in fact have left this to the reader to further explore before carrying out such therapeutic intervention.

The chapters on behavioral-medical management in chronic pain and rehabilitation in chronic pain are reasonably good. They are, however, too short to be of significant use to those who wish to enter this area of anesthesia. Nevertheless, these chapters bring out the importance of psychology in chronic pain management.

The chapter on controversies in chronic pain management succeeds in listing a number of controversial topics but also adds a good deal of the author's feelings that at times verge on confused thinking. An example is the warning on page 640 that healthy skepticism is needed regarding whether epidural steroids are given more for economic reimbursement purposes than for well-defined medical indications. Between World Wars I and II there was a 200% increase in lower back pain in the United States concomitant with the introduction of the Workmens Compensation patient insurance program. The author then goes on to describe the physician's fee rates, but fails to mention that epidural steroids were in fact not introduced on any scale for some 20–25 years later. Unfortunately, the author also fails to mention that epidural steroids in fact have saved an enormous amount of unnecessary surgery and suffering that, in the end, cost even more. The author quite correctly includes thermography as one of the areas of controversy. Thermography has more controlled studies than the much more accepted EMG that he does not pick on. In fact, EMG has a higher failure rate than thermography by the listed references.

The chapter on organization and operation of a comprehensive pain management center is indeed good and useful. However, more emphasis should be placed on the role of anesthesia, not only in outpatient- and rehabilitation-type activities and simple block procedures, but in the combination of outpatient and inpatient services rendered by the anesthesiologist. A dangerous role that anesthesiologists can drift into is just to be a "block physician" or play second fiddle to behavior modification-related and rehabilitation-type activities only.

In summary, this small book on chronic pain indeed is neither concise nor a comprehensive guide for the practicing anesthesiologist but is useful bedtime reading for the discriminating and experienced individual who knows a sufficient amount to avoid pitfalls that unfortunately have escaped editorial scrutiny. This reviewer certainly does not

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feel that this is the way to start an anesthesiologist-in-training. The book is recommended with that in mind.

Gabur R. Racz, MD
Texas Tech University Health Sciences Center
Lubbock, Texas

Anesthesia for Ambulatory Surgery

Bernard V. Wetchler, ed. Philadelphia: J.B. Lippincott, 1991, 690 pp, $69.50.

This second edition, essentially an updated and expanded revision of the 1985 original version, is edited by Dr. Bernard Wetchler who has been instrumental in establishing anesthesia for outpatient surgery as a bona fide subspecialty. Covering virtually all aspects of outpatient surgery, this edition maintains the book's stature as one of the field's two primary texts.

The 10 chapters are written by a mix of academic and private anesthesiologists, lawyers, hospital administrators, and professional consultants. This diversity of background promotes balance and accurately reflects the various elements of successful outpatient anesthesia and surgery. In particular, the chapters on patient/procedure selection and problem solving in the postanesthesia care unit are complete and well written. The chapter on the pediatric patient covers everything from the "problem" child to psychological preparation to pain management techniques. In contrast, the chapter on the adult and geriatric patient is unwieldy. Readability would have been enhanced had it been separated into smaller parts. For example, information about conscious sedation is buried in this chapter, and the well-written segment on the geriatric patient deserves its own chapter. To its credit, anesthetic recipes are avoided and obvious effort is made to give referenced debate to the various drugs and techniques.

Two chapters deserve special mention. The chapter on complications uses a case report format to illustrate more effectively the different types of complications that occur after outpatient anesthesia and surgery. The chapter entitled "In the Real World" is an extremely well-done and completely indexed discussion of many of the common clinical dilemmas faced in outpatient surgery. Here again, case reports are used to cover such topics as the "ex-premie," malignant hyperthermia, postdural puncture headache, and antibiotic prophylaxis.

In addition to the well-written chapters noted above, the book shines when dealing with the non-anesthesia-related elements of outpatient surgery. These include a chapter on the past, present, and future of ambulatory surgery, a chapter on legal implications and standards, and a three-part chapter on planning, marketing, and the fundamentals of a successful outpatient facility. These sections are particularly useful because they present information that is difficult for the anesthesiologist to find.

Forms and policies seem to be a hobby for those of us in outpatient surgery! The last section in the book provides more than 60 pages of sample forms and policies from private and academic outpatient facilities. These provide more-than-adequate samples for the reader who needs to design custom forms.

On a critical note, a few sections of the text are distinguished by being printed on grey paper, which unfortunately makes the text difficult to read. Similarly, the tables are reproduced in small, regular typeface, whereas the boldface headings of the first edition made the tables more noticeable.

Resident anesthesiologists will find this edition an easy-to-read and complete overview of outpatient anesthesia and surgery. Those in private practice will find it a very useful reference.

Martin S. Bogetz, MD
University of California
San Francisco, California

Opioids in Anesthesia II

F. G. Estafanow, ed. Stoneham, Massachusetts: Butterworth-Heinemann, 1990, 331 pp, $45.00.

Opioids in Anesthesia II is the edited version of the presentations at a symposium of distinguished researchers and clinicians with a strong background in the development and use of opioids for anesthetic practice. There are 50 authors for 25 chapters and nine named discussants as well as brief comments from numerous participants at the symposium. The purpose of the symposium and the book is to present "the results of the most recent research and clinical experience with opioids in anesthesia and pain management." The book as a whole is, in fact, very current and is divided into four major sections: Scientific Basis, Clinical Applications, Delivery Methods, and Issues.

The section on the scientific basis of opioid usage, primarily of interest to researchers, is an up-to-date, state-of-the-art review of opioid biochemistry, peptides, receptors, and cellular and subcellular actions and can be described as reviews of experimental evidence that "may ultimately have direct consequences in the practice of clinical anesthesiology." For this reviewer at least, this section had to be read slowly and methodically to be understood. However, most of the authors of the six chapters in this section, which makes up about one-third of the book, make an effort to describe the clinical relevancy of their presentation in the last portion of their chapters. On the whole, these latter parts of the chapters and the discussions that follow are very readable and interesting to the clinician, but despite this fact, most anesthesia practitioners would be advised to start with section II of the book so as not to be discouraged and then return to the scientific basis section if they are so inclined.

The chapters in the section on clinical applications, comprising about half of the text, vary from good to excellent in readability and clinical interest. The introductory chapter, Clinical Perspectives of Opioid Anesthesia, is excellent. The section also includes chapters on the use of opioids for cardiac and obstetrical patients, as well as for neuroanesthesia, peripheral vascular surgery, and pediatric and same-day surgery. There is a very good review of monitored anesthesia care. Other chapters include monitoring of the adequacy of anesthesia, a report on epidural sufentanil for cancer pain, and a chapter on mechanisms and therapy for postoperative myocardial ischemia. The last chapter in the second section concerns the use of transdermal fentanyl in the management of cancer pain. There is a good discussion of the rationale and basis for transdermal opioids as well as its advantages and disadvantages. The discussion at the end of part II is apparently an unedited, somewhat disjointed, transcript of the meeting consisting mainly of many people trying to make their own specific points, some of which are reasonable and some of which have little clinical relevance.

The third section, on delivery methods, is again a very readable section for the clinician. The reviews on pharmacokinetics and pharmacodynamics, particularly in the chapter on continuous infusions, are well done. The chapter on transmucosal delivery reviews the history of mucosal delivery and gives a balanced view of what might be expected for the future. The chapter on the clinical overview of transdermal fentanyl is well done but somewhat redundant after the previous transdermal fentanyl chapter in part II. The last chapter of this section is on patient-controlled analgesia and is possibly too inclusive. There is a good review of the rationale for the PCA and its use, but too much space is devoted to the particular types of hardware available.

The fourth section, Issues, has only three chapters, which all relate in some manner to opioid abuse and/or addiction. The last chapter actually deals with malpractice cases and its relation to the rest of the book is tenuous. Nonetheless, it is of interest to the clinician. The other two chapters are very timely and could be helpful to individuals or to clinical departments where drug abuse is always a potential problem.

Because of the manner of its conception (the result of a symposium), the chapters are somewhat uneven in quality or applicability but generally good and there is some duplication. However, the book is well referenced, has reasonable illustrations and tables, and updates one on the uses of and the rationale for the uses of opioids now and in the near future. This book provides valuable and interesting reading for both clinicians and researchers who wish to expand their knowledge of opioids and is a reasonable addition to their personal library.

Michael Murphy, MD
Crawford Long Hospital of Emory University
Atlanta, Georgia

Clinical Anesthesia in Neurosurgery

E. A. M. Frost, ed. Stoneham, Massachusetts: Butterworth-Heinemann, 1991, 593 pp, $98.00.

This second edition, published six-plus years after the first edition, contains contributions by 25 authors, revisions of some chapters, and some new chapters. Dr. Frost is the author or a coauthor of nine of the 25 chapters. Eleven authors are anesthesiologists, 12 are surgeons, one is a radiologist, and one is a lawyer. Thirteen authors are associated with Montefiore Medical Center and/or Albert Einstein Medical Center.

Following a Foreword, Prefaces, and an Introduction, the book is divided into five sections (percentage of total text in parentheses after each section): Cerebral Physiology and Evaluation (28%), Neurosurgical and Related Procedures (38%), Central Nervous System Trauma (17%), Postoperative and Intensive Care (11%), and Cerebral Death (2%). The remaining 4% are miscellaneous pages. Figures and photographs are black and white, with a number of the drawings being original with this edition. Although the photographs are designed to be helpful contributions to the text, a number of the photographs are quite dark, making it difficult to visualize some features.

Although this text is multiauthored, the reader is not hampered by marked differences in writing style, and the majority of the book reads relatively easily. As with other multiauthored texts, there is some redundancy. For example, management of the patient with an intracranial tumor is discussed in the chapters "Posterior Cranial Fossa Surgery," "Intracranial Tumors," and "Pediatric Neuroanesthesia." Intracranial pressure and intracranial hypertension are discussed in the chapter "Intracranial Pressure," as well as the chapters addressing intracranial tumors, head injury, and major brain insult. The index is well-done and facilitates locating a particular topic that is discussed in more than one location in the book.

The number of references per chapter varies from 25 to 274. Some sections reflect the authors' opinions, others are referenced minireviews. References through 1988 were found. Information provided in this text should be useful to residents and others interested in neuroanesthesia. At $98.00 a copy, the buyer will need to decide whether to purchase this book or one of the other neuroanesthesia texts.

Joseph M. Messick, Jr, MD
Mayo Clinic
Rochester, Minnesota

Studies of Narcosis

C. E. Overton, 1901. English translation edited by R. L. Lipnick. London: Chapman and Hall, and Park Ridge, Illinois: Wood Library-Museum of Anesthesiology, 1990, 203 pp, $65.00.

In 1989 the Wood Library-Museum initiated a series of translations into English of seminal materials of importance in anesthesiology that previously existed only in some other language. The first, edited and translated from the French by Dr. B. Raymond Fink of the Department of Anesthesiology at the University of Washington in Seattle and published in 1989, was Claude Bernard's 1875 "Lectures on Anesthetics and on Asphyxia" (originally "Leçons sur les Anesthésques et sur L'Asphyxie"). The present translation, that of Overton's "Studien über die Narkose," is the second in that series. A long overdue contribution to anesthesiology, this translation has been beautifully edited by Dr. Robert Lipnick of the Office of Pesticides and Toxic Substances, a division of the United States Environmental Protection Agency.

The author of *Studies of Narcosis*, Charles Ernest Overton (1865–1933), was born in Cheshire, England. At the age of 17 he moved with his parents to Zurich where, in 1889, he received his Ph.D. in botany from the University of Zurich. In 1907 Overton became professor and head of pharmacology at the University of Lund in Sweden, where he resided until his death in 1933. Curiously, Overton adopted German as his language so thoroughly and forsook English so completely that, it has been said, he became unable to understand English, his native language, written or oral. He certainly did well in German, however, as testified to by the international respect afforded this and others of his publications by his contemporary peers. Indeed, Overton became one of the outstanding scientists of his time. *Studies of Narcosis*, one of his several major contributions, describes in exquisite detail how he came to establish the relationship between lipid solubility of non-ionized organic and inorganic compounds and their anesthetic potential. His work, combined with similar simultaneous and independent observations reported in Germany by Hans H. Meyer, led to what is now widely referred to as the Meyer-Overton theory of anesthesia.

Overton made a major contribution to the understanding of anesthetic action. The primary focus of his research was, however, the plasma, i.e., cell membrane. In 1899, for example, he published a treatise describing factors involved in determination of cellular permeability, the so-called Overton Rules. The establishment was and is considered as important and signal a contribution as we in anesthesiology consider his *Studies of Narcosis*. Overton was a leading expert of function and even structure of plasma membranes at a time when many still doubted the existence of such a structure, in part because in the 1890s it was microscopically invisible. In addition, Overton also developed the first data relating molecular structure to pharmacologic (or toxic) effect. He made all his many contributions by essentially never ending, meticulous studies of the effect of osmotic pressure and all sorts of chemical compounds on plant cells and on whole animals. The latter centered on tadpoles because he recognized the need to study toxicity and pharmacologic effects only when animals were exposed to concentrations of the compounds that remained constant despite uptake into intact organisms, an environment easily achieved by placing tadpoles in aqueous solutions of volumes so large that uptake had trivial, if any, effect on concentration. That anesthetized tadpoles do not run the risk of developing airway obstruction might have been helpful too.

It was the transdisciplinary value of the data in Overton's *Studies of Narcosis* and Dr. Lipnick's recognition of the value of Overton's data as a basis for, inter alia, estimating hazards associated with entry of potentially toxic commercial organic compounds into the environment, especially into rivers and other aqueous environments, that convinced the EPA to contract for the translation of Overton's book. The importance and the uniqueness of the data in Overton's book were why the Wood Library-Museum undertook the financing of publication of Dr. Lipnick's edited translation. For the same reasons, the decision was made to have it published in England by a publisher experienced in distribution and promotion of such a transdisciplinary monograph throughout the Continent and the United Kingdom, while the Wood Library-Museum assumed responsibility for handling in the North American market.

The relevancy of this translation of Overton's book is amply described in the Introductions in this book provided by Dr. Keith Miller of Harvard Medical School, by Drs. Peter Winter and Leonard Firestone of the University of Pittsburgh, and by Dr. Lipnick himself. The value of this material is further advanced by inclusion in the index of today's official names of all compounds mentioned by Overton, thereby assuring their accurate identification. Also included are appendices that provide a list of all of Overton's publications as well as articles about Overton and his work.

This is a book, a translation, that every anesthesiologist should at the very least scan, if not read from cover to cover. It is a book that allows one to understand the genesis of one of the most basic aspects of our specialty, not only for its historical significance but for its present day, continuing relevancy. The book is a monument to the ability of a sharp intellect to produce new, important, and valid information using little more than finely honed powers of observation, an ability as important then as it is now.

Nicholas M. Greene, MD
Yale University
New Haven, Connecticut

Anesthetic and Obstetrical Management of High Risk Pregnancy

Sanjay Datta, ed. St. Louis: Mosby Year Book, 1990,
719 pp, $79.00.

This book has a global aim of collating anesthetic and obstetric management for the high-risk parturient into a single text. Each of the 30 chapters has either one, two, or three authors for a total of 62 authors drawn from anesthesiology and obstetrics or a pertinent specialty like neurology. The 30 chapters take the reader through prepartum and intrapartum fetal and maternal physiologic and pathophysiologic changes of disease processes affecting obstetric and anesthetic patient management decisions.

Although all the chapters are relatively current, that is, a majority of citations are no more than 5 years old, some chapters lean heavily on older references. The chapters on the pregnant teenager, the diabetic parturient, pregnancy-induced hypertension, and substance abuse are thoughtfully presented and should be useful to all professional levels dealing in these areas. The subjects of febrile parturient, fetal distress, and intrauterine fetal death are difficult ones, at best, as is evident by the varying opinions or lack of opinions and data provided in the chapters. However, in this litigious age, the physician must be aware of the data that do exist in these areas.

The chapter on orthopedic problems should have addressed the pseudo-disc syndrome of pregnancy, which has caused some mothers to undergo unnecessary termination of their pregnancies to become subjects for laminectomy. The chapter on emboli in pregnancy is particularly weak in its lack of reference to Steve Clark's work in amniotic fluid embolism.

Overall, this book is a wealth of tidbits of physiologic and pathophysiologic data not found in the standard texts. The multiplicity of authors must have been a nightmare for the editor. The differences in phraseology and style make the text read in a slightly bumpy manner. However, Dr. Datta must be commended for bending much of the "Americanese" to English. This text should be available in all obstetric units dealing with high-risk pregnancies, in all teaching units, and in the personal libraries of obstetric anesthesiologists and perinatologists.

Thomas H. Joyce III, MD
Baylor College of Medicine
Houston, Texas

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Bell C, Hughes CW, Oh TE, eds. *The Pediatric Anesthesia Handbook.* St. Louis: Mosby Year Book, 1991, 626 pp, $34.95.

Bennett HJ, ed. *The Best of Medical Humor.* Philadelphia: Hanky & Belfus, 1991, 228 pp, $25.00.

deBruijn NP, Clements FM. *Intraoperative Use of Echocardiography.* A Society of Cardiovascular Anesthesiologists Monograph. Philadelphia: J.B. Lippincott, 1991, 225 pp, $49.95.

DeCastro J, Meynadier J, Zenz M, eds. *Regional Opioid Analgesia.* Boston: Kluwer Academic Publishers Group, 1991, 633 pp, $195.00.

Eichhorn JH, ed. *Improving Anesthesia Outcome.* Volume 5, No. 2 in Problems in Anesthesia series. Philadelphia: J.B. Lippincott, 1991, 181 pp, $70.00.

Max MB, Portenoy RK, Laska EM, eds. *The Design of Analgesic Clinical Trials.* Volume 18 in Advances in Pain Research and Therapy. New York: Raven, 1991, 751 pp, $122.00.

Roberts JT, ed. *Fiberoptics in Anesthesia.* Anesthesia Clinics of North America, Volume 9, No. 1. Philadelphia: W.B. Saunders, 1991, 198 pp, $74.00 annual subscription for four issues or $32.00 each issue.

Warfield CA, ed. *Manual of Pain Management.* Philadeliphia: J.B. Lippincott, 1991, 384 pp, $49.50.

A Guide for Authors

Manuscripts should be sent to:

Ronald D. Miller, MD
Editor-in-Chief
Anesthesia and Analgesia
3497 Sacramento Street
San Francisco, CA 94118

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Anesthesia and Analgesia, the oldest publication for the specialty of anesthesiology, is the official voice of the International Anesthesia Research Society. It publishes original articles, clinical reports, technical communications, review articles, and letters to the editor.

All papers are reviewed by three or more referees. Acceptance is based on significance, originality, and validity of the material presented. Only one copy of an article not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a covering letter that includes a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *The New England Journal of Medicine* 1991;324:424–8.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, from parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

General

☐ Original articles describe in 3000 words or less clinical or laboratory investigations.

☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.

☐ Technical communications are papers that deal with instrumentation and analytic techniques.

☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.

☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double-spaced, and a title and three copies must be provided.

☐ Type manuscripts on white bond paper, 216 by 279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 25 mm (1 in.) using double-spacing throughout.

☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

☐ Submit original plus three copies of the manuscript and four sets of figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter and by letters granting permission to reproduce previously published materials or to use illustrations that may identify subjects.

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☐ The title page should contain the title of the article, which should be concise but informative;

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☐ First name, middle initial, and last name of each author, with highest academic degree(s); each listed author must (a) have participated in the work to the extent that he or she could publicly defend its contents; (b) have read the manuscript before its submission for publication; and (c) be prepared to sign a statement to the effect that he or she has read the manuscript and agrees with its publication;

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Abstract and Key Words

☐ The second page should carry an abstract of not more than 150 words. (Abstracts are not needed for Clinical Reports.)

☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.

☐ Define all abbreviations except those approved by the International System of Units.

☐ Key (indexing) words: Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article.

Text

☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the following headings: Introduction, Methods, Results, and Discussion.

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☐ *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references and do not review the subject extensively.

☐ *Methods:* Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

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☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.

☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data.

☐ *Units of measurement:* Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in **SI units** with, if desired, present conventional metric units in parentheses.

References

All references must be available to all readers. Cite only references to books and articles or abstracts published in peer-reviewed *Index Medicus* journals. Abstracts appearing only in programs of meetings are not acceptable, nor are abstracts more than five years old.

☐ Number references consecutively in the order in which they are first mentioned in the text.

☐ Identify references in text, tables, and legends by arabic numerals (in parentheses, on line)

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☐ The titles of journals must be abbreviated according to the style used in *Index Medicus*.

☐ References must be verified by the author(s) against the original documents, and the entire list must be checked for nonduplication.

Examples:

1. *Standard journal articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
   Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 1991;72:275–81.
2. *Personal author(s) of books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974.
3. *Chapter in a book*
   Weinstein L, Swartz NM. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

Tables

☐ Type each table double-spaced on a separate sheet. Do not submit tables as photographs.

☐ Number tables consecutively and supply a brief title for each. Give *each* column a short or abbreviated heading.

☐ Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use lower-case italicized letters in alphabetical order.

☐ Do not use internal horizontal or vertical rules.

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☐ Submit four complete sets of figures. Figures should be in black and white only and be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Note: Art work of published articles will not be returned.

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☐ At first mention in text, spell out in full and follow immediately with the abbreviation (enclosed within parentheses).

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☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 5th ed. Bethesda, Maryland: Council of Biology Editors, 1983;
2. American Medical Association. Manual of style. 8th ed. Baltimore, Maryland: Williams & Wilkins, 1989.

Exclusive Publication Statement

☐ The principal author of all materials submitted for publication (except letters to the editor) must include in a covering letter a statement to the effect that none of the material in this manuscript has been published previously nor is any of this material currently under consideration for publication elsewhere.

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Anesthesiologist to join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approx. 40,000 (35 mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 624C/H.

624C/H

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643D/G

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653D/G

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659E/G

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Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

674E/D

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The Pain Consortium of Greater Kansas City is offering a 12-month fellowship in pain management. This is a unique training opportunity for a highly motivated, patient-oriented anesthesiologist to participate in a strong clinical pain management program. Emphasis is on comprehensive evaluation and the use of neural blockade in the treatment of acute, chronic, and cancer pain. Training in interventional pain management techniques including implantable drug delivery systems and CT-guided neurodestructive procedures is integrated with strong individual clinical teaching.

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689FG

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701G/L

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702G

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CONTRAINDICATIONS: None known.

WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more suitable for these patients.

PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.

Renal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.

Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.

Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.

Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.

Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.

Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate anesthesia.

Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.

Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.

Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section.

Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a µg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED$_{95}$. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed; therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T_1 to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.

ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:

Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.

Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.

Musculoskeletal: muscle atrophy, difficult intubation.

Nervous: hypesthesia, CNS depression.

Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.

Skin and Appendages: rash, urticaria.

Urogenital System: anuria.

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After Reconstitution: When reconstituted with bacteriostatic water for injection, USP: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

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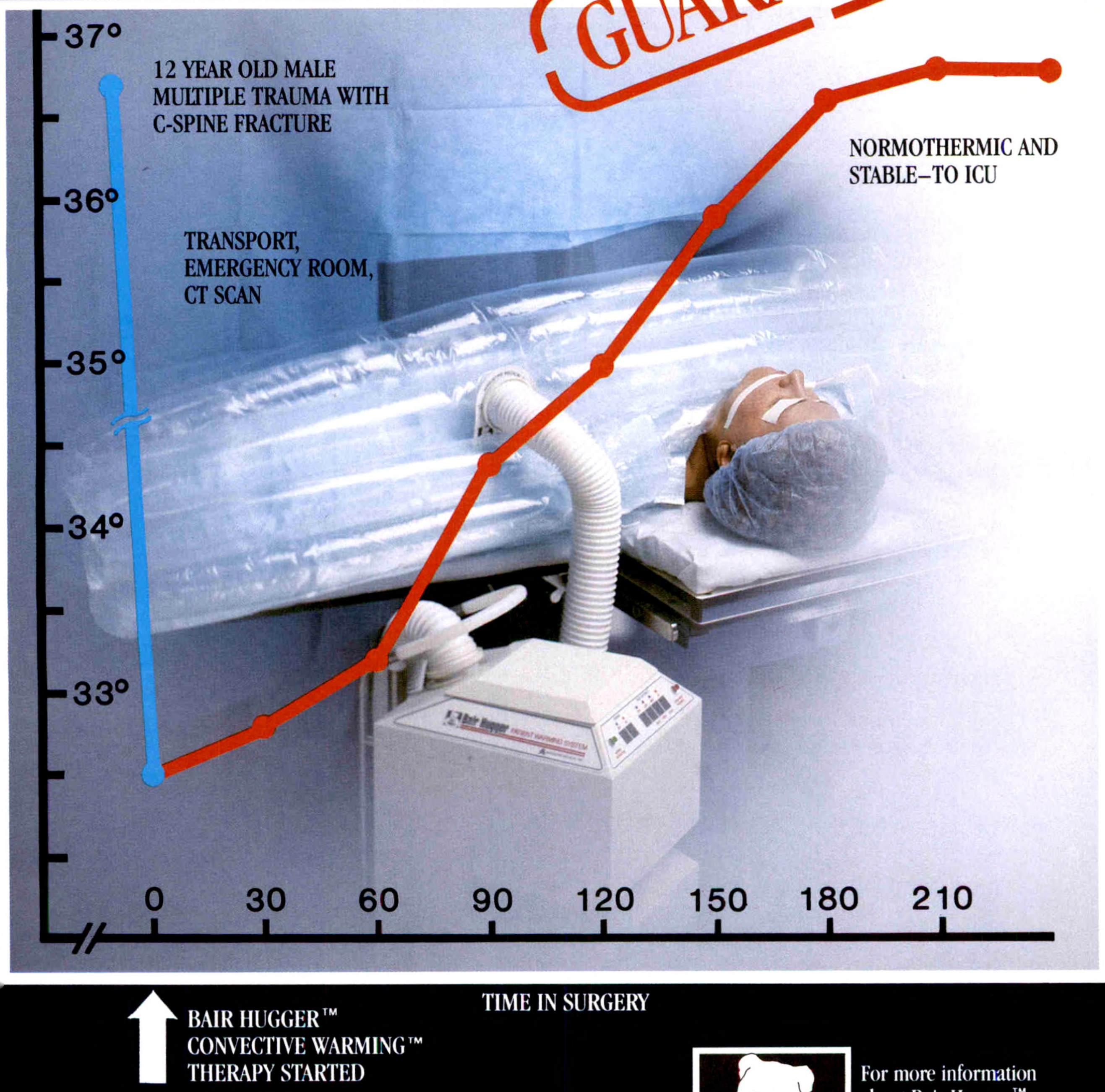

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Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. *© 1991 by the International Anesthesia Research Society.* *Second class postage paid at New York, NY and at additional mailing offices. Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year; in all other countries, $110.00. (See General Information in this issue for further details regarding membership.) Subscription information for 1991 applying to non-IARS members: Institutions, $140.00; nonmember individuals, $100.00. Outside the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico; $55.00 for surface airlift to Europe; $75.00 for surface airlift to Japan; and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: Anesthesia and Analgesia, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.*

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Journal of the International Anesthesia Research Society

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Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1991 by the International Anesthesia Research Society. Second class postage paid at New York, NY and at additional mailing offices.

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Single issues: Single copy information is available from Elsevier Science Publishing Co., Inc., upon request. Back volume (all issues prior to 1983) information is available from the IARS.

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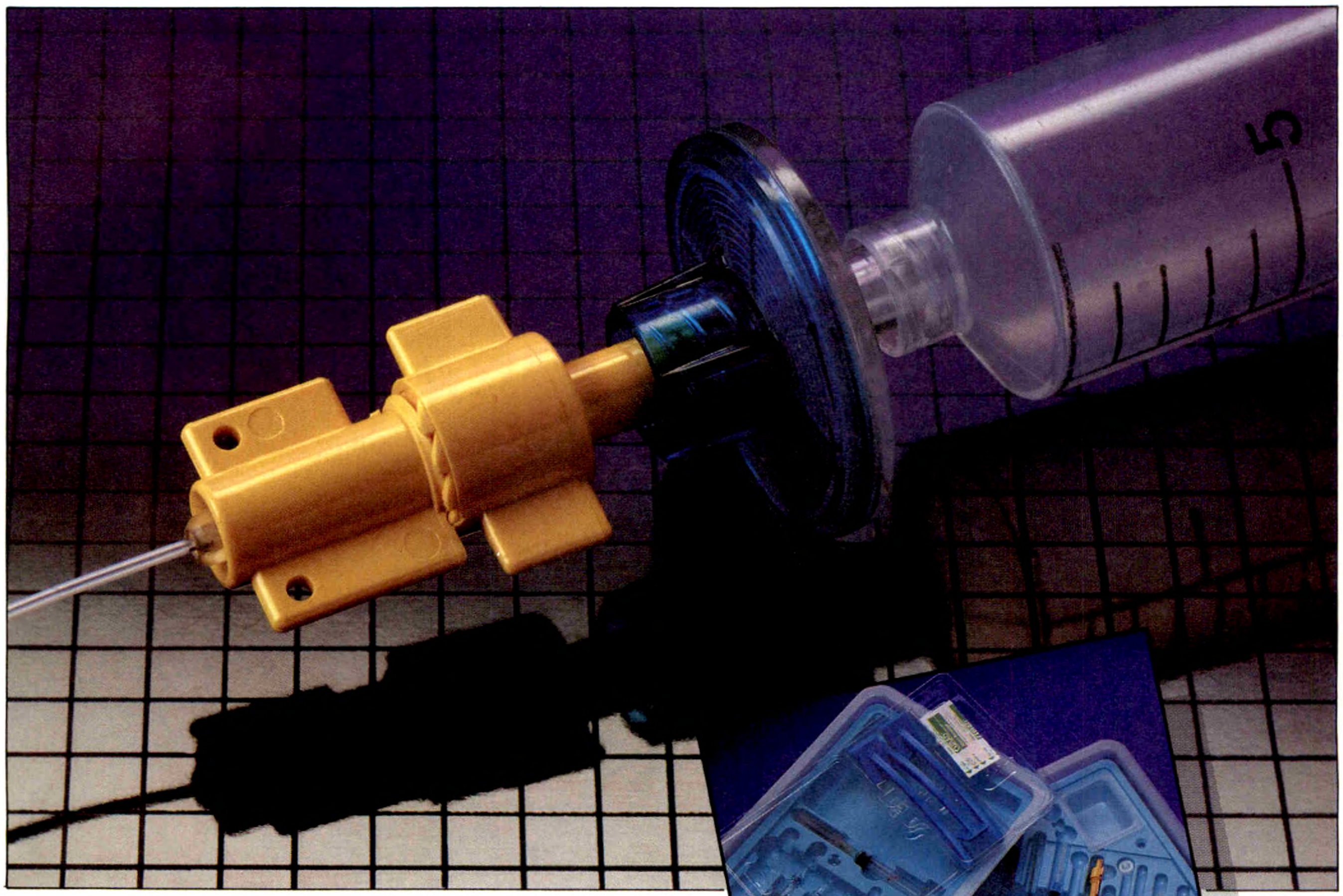

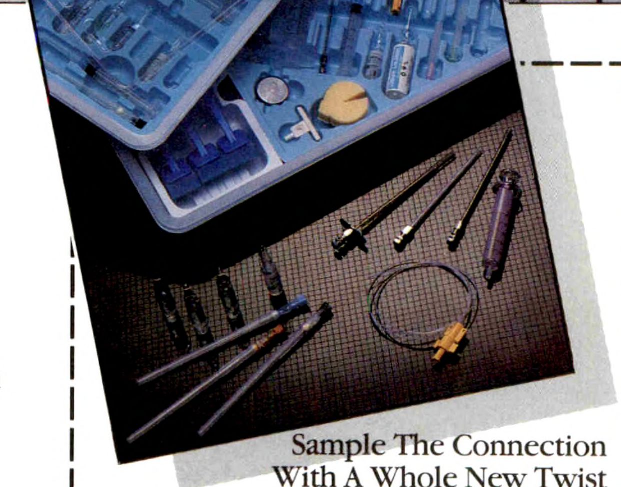

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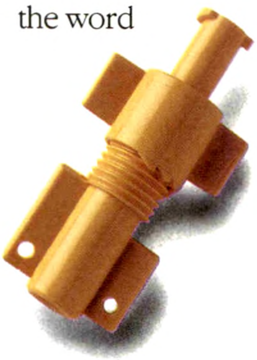

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The Logical Choice

Crucial Parameters in Selecting a Neuromuscular Blocking Agent

	Norcuron® (vecuronium bromide) for injection	Atracurium besylate
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance.[1]	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance.[1] ($P<.05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma)[5]
RECOVERY		
To 25% of control	25–45 min[3]	35–45 min[5]
To 95% of control	45–65 min[3]	60–70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08–0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4–0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.*[2,5,7]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.† Can be reconstituted with various IV solutions including Lactated Ringers.‡	2-year shelf life under constant refrigeration.† Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

*Dose of atracurium above 0.5 mg/kg is not recommended.
†As originally supplied by the respective manufacturers.
‡Storage after reconstitution varies with solution. See package insert.

Norcuron®

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Norcuron®
(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

> **THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.**

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

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VERSED®

midazolam HCl/Roche Ⓒ IV

FIRST

Dosing considerations

Individualize dose. Consult complete product information under DOSAGE AND ADMINISTRATION for specific dosing recommendations in the elderly and/or debilitated and for patients receiving narcotic or other CNS depressants. VERSED can be administered concomitantly with most other commonly used premedicants, including reduced doses of narcotics.

VERSED is available in 1 mg/mL and 5 mg/mL strengths.
Please see summary of product information on following page.
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VERSED®
(midazolam HCl/Roche) ⒸIV
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic. Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant. 3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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Roche Laboratories
ROCHE
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340 Kingsland Street
Nutley, New Jersey 07110-1199

Perioperative Maternal and Neonatal Acid-Base Status and Glucose Metabolism in Patients With Insulin-Dependent Diabetes Mellitus

Sivam Ramanathan, MD, Pancy Khoo, MD, and James Arismendy, BS
Department of Anesthesiology, New York University Medical Center, New York, New York

Maternal and neonatal acid-base status and glucose metabolism were studied in 20 patients with insulin-dependent diabetes mellitus (group 1) undergoing elective cesarean section under lumbar epidural anesthesia. All patients were given glucose/insulin infusion before delivery. Fifteen healthy patients with iatrogenic hyperglycemia (group 2) and 15 healthy euglycemic patients (group 3) served as controls. Results were expressed as mean ± 1 SE and were analyzed using analysis of variance and χ^2 analysis at $P < 0.05$. No significant differences were seen at delivery either in maternal arterial and neonatal umbilical venous and arterial blood acid-base status or in neonatal Apgar scores among the three groups. Patients in groups 1 and 2 had larger blood glucose concentrations than those in group 3 ($P = 0.01$). Diabetic mothers and their neonates had a 25%–50% reduction in pyruvate concentration in maternal venous, and neonatal umbilical venous and arterial blood compared with that in the other two groups ($P = 0.001$). Postpartum neonatal hypoglycemia (<30 mg/dL) developed in seven of the group 1 neonates ($P = 0.05$). Thus, epidural anesthesia in diabetic women is associated with normal acid-base status in the mother and in the neonate. The data also show an increased incidence of neonatal hypoglycemia and altered maternal and neonatal glycolysis in patients with diabetes mellitus.

(Anesth Analg 1991;73:105–11)

Regional anesthesia is widely used for cesarean section in patients with insulin-dependent diabetes mellitus. Previous studies have described the effects of regional anesthesia on the acid-base status of infants born of diabetic mothers (1–3). One of these studies noted that spinal anesthesia was associated with increased fetal acidosis in diabetic pregnancies (1). However, the mothers were given large volumes of glucose-containing solutions intravenously before delivery that may have decreased the fetal blood pH in this study (4). A subsequent study by the same authors did not find evidence of fetal acidosis with spinal anesthesia when glucose-free intravenous fluids were used (2). A third study reported the effects of epidural anesthesia on umbilical artery blood pH. This study also used intravenous glucose-containing solution (3). None of these studies provided information on maternal, fetal, and neonatal glucose homeostasis known to be abnormal in diabetic parturients (5). This study evaluates maternal and neonatal acid-base status, glucose homeostasis, and glycolysis in diabetic patients given nonglucose solutions before lumbar epidural anesthesia for elective cesarean section. To elucidate to what extent the hyperglycemic state may contribute in diabetic patients to any of the abnormalities in glucose homeostasis in the mother and the neonate, two types of controls were studied: healthy patients with intentional iatrogenic hyperglycemia and euglycemic patients.

Methods

The study protocol was approved by the Institutional Review Board of the New York University Medical Center and informed consent was given by the patients. A total of 50 patients were studied. They were divided into three groups: group 1 consisted of 20 patients with insulin-dependent diabetes mellitus. Groups 2 and 3 each consisted of 15 healthy patients. Patients in group 2 were given glucose infusion before delivery to produce iatrogenic hyperglycemia and those in group 3 remained euglycemic before delivery. The diabetic patients were scheduled for elective cesarean section at 37–39 wk, and the healthy

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Accepted for publication April 30, 1991.

Address correspondence to Dr. Ramanathan, Department of Anesthesiology, New York University Medical Center, 560 First Avenue, New York, NY 10016.

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0003-2999/91/$3.50

Table 1. White Severity Classification of Diabetes Mellitus and Preoperative Insulin Therapy

	No. of patients
Type of diabetes mellitus	
Class B	8
Class C	4
Class D	2
Class F	1
Class R	5
Preoperative insulin therapy	
Insulin pump	3
Regular insulin	2
Regular + Isophane	12
Isophane	2
Regular insulin + Lente	1

Class B, duration of diabetes <10 yr; class C, duration of diabetes >10 yr; class D, benign retinopathy; class F, diabetic nephropathy; class R, malignant proliferative retinopathy.

patients were scheduled for a second elective cesarean section at term.

The diabetic patients ($n = 20$) were managed by a diabetologist during pregnancy. All patients measured their own capillary blood glucose with a glucometer, and they self-administered insulin at home. The severity classification of diabetes and the prenatal insulin therapy are given in Table 1. The following hospital protocol was used to guide perioperative insulin therapy. Patients were allowed oral food intake until 4 AM on the morning of operation, which was scheduled for 9 AM. They received their usual insulin dosage until the night before operation. A glucose/insulin infusion at a rate of 70 $mg \cdot kg^{-1} \cdot h^{-1}$ of glucose and 1 U/h of insulin was started at 6 AM (6). The insulin (diluted in normal saline solution) and glucose (5% dextrose in water) were administered using independent constant infusion pumps. The maternal capillary blood glucose value was measured using glucose oxidase strips (Chemstrip BG, Boehringer, Mannheim Corporation, Indianapolis, Ind.) and a reflectance glucometer (Accu-Check II, Boehringer, Mannheim Diagnostics, Indianapolis, Ind.) every 30 min. All glucometer measurements were made by a previously trained nurse from the diabetic clinic of the hospital. Insulin infusion rate was adjusted between 0.5 and 2 U/h to maintain a maternal capillary glucose level between 70 and 120 mg/dL (6). Hyperglycemia greater than 140 mg/dL was treated with intravenous administration of 2 U of regular insulin, and hypoglycemia less than 60 mg/dL was treated with intravenous administration of 2–5 g of glucose.

Lactated Ringer's solution (1200 mL) was infused in 1 h before the induction of anesthesia. A lumbar epidural catheter was inserted into the L2-3 interspace, and sensory level was induced to the T6-4 level by using 5-mL increments of 0.5% bupivacaine. Left uterine displacement was maintained, and the patients breathed oxygen from a disposable face mask at a fraction of inspired oxygen of 0.5. Maternal blood pressure was measured every minute using an automatic instrument (Dinamap Vital Signs Monitor, Critikon Inc., Tampa, Fla.). Any maternal systolic hypotension less than 100 mm Hg was treated with 5-mg increments of ephedrine. At delivery, the maternal capillary blood glucose level was measured with the glucometer. In addition, maternal venous, and neonatal umbilical venous and arterial blood glucose, lactate, and pyruvate levels were measured enzymatically in the laboratory in heparinized whole blood (7). The glucose level was measured by the hexokinase method (7,8) standardized against solutions containing 50, 100, 150, 200, or 250 mg/dL of glucose. In addition, maternal arterial and neonatal umbilical venous arterial blood oxygen tension (Po_2), carbon dioxide tension (Pco_2), and pH were measured. Blood base-excess was calculated using Severinghaus' equation (9). Skin incision to delivery time, uterine incision to delivery time, and neonatal Apgar scores and birth weight were noted. Neonatal capillary blood glucose level was measured in heel-stick samples at birth and once every hour by the nurses in the nursery; and a blood glucose level less than 30 mg/dL was treated with 15 mL of 10% oral glucose solution. Hypoglycemia was confirmed by simultaneous hospital laboratory measurement of peripheral venous glucose. Excess lactate (portion of the lactate that cannot be accounted for by the measured pyruvate level) was calculated using Huckabee's equation (7,10).

The remaining 30 healthy patients were alternately assigned to either group 2 or group 3. Patients assigned to group 2 ($n = 15$) were given 800 mL of lactated Ringer's solution plus 400 mL of 5% dextrose in water (20 g of glucose) over a period of 1 h before induction of epidural anesthesia. Glucose administered to healthy mothers at a rate of 20 g/h is unlikely to alter maternal or neonatal acid-base status or to increase the incidence of neonatal hypoglycemia (7). The patients assigned to group 3 ($n = 15$) were given 1200 mL of lactated Ringer's solution before epidural anesthesia. The study protocol was the same in group 2 and 3 patients as in group 1 patients, except that they were not given insulin prepartum or intrapartum and that the maternal or neonatal capillary blood glucose level was not measured at delivery.

Results were expressed as mean ± 1 SE. Analysis of variance was used to test differences in interval data among the three groups at $P < 0.05$. When analysis of variance showed a significant F value, a protected least significance difference method was used to make intergroup comparisons at the 5% error level

Table 2. Maternal Vital Statistics, Birth Weight, Apgar Scores, and Neonatal Hypoglycemia

	Group 1 (Diabetic)	Group 2 (Hyperglycemic)	Group 3 (Normoglycemic)
Mother			
No. of patients	20	15	15
Age (yr)	31 (0.9)	32 (2)	29 (1)
Height (cm)	160 (2)	162 (4)	161 (3)
Weight (kg)	79 (6)*	72 (3)	71 (4)
ID interval (min)	22 (3)	26 (3)	25 (3)
UD interval (min)	2.1 (0.3)	2.8 (0.6)	2.7 (0.5)
Ephedrine therapy	2	1	2
Total ephedrine dose (mg)	10	5	5
Baby			
Birth weight (kg)	3.435 (0.13)	3.31 (0.134)	3.605 (0.101)
Apgar score <7 (1 min)	1	1	1
Apgar score <9 (5 min)	1	1	1
Hypoglycemia (No. of babies)	7*	1	0

ID interval, skin incision to delivery time; UD interval, uterine incision to delivery time.
Figures within parentheses represent 1 SE.
*Significantly different from groups 2 and 3 ($P = 0.05$).

(11). Nominal data were analyzed using contingency table analysis. For statistical analysis, Complete Statistical System (CSS, Statsoft, Inc., Tulsa, Okla.) computer software was used.

Results

Maternal Vital Statistics, Neonatal Complications, and Maternal and Neonatal Acid-Base Status

No statistical differences were noted among the three groups with respect to maternal age and height, skin incision to delivery time and uterine incision to delivery time, the number of patients requiring ephedrine for hypotension, the total ephedrine dose, and the neonatal birth weight and Apgar scores (Table 2). The diabetic patients were significantly heavier than the healthy patients (Table 2). Hypoglycemia did not develop in any diabetic mother before delivery. Five patients required one supplemental injection of insulin, and two others required two injections for capillary glucose of 155 ± 4 mg/dL (range 144–163 mg/dL) before delivery. Hypoglycemia developed in seven neonates from group 1, in 1 from group 2, and in none from group 3 ($P = 0.05$, Table 2). Of the seven neonates in whom hypoglycemia developed in group 1, five were born to mothers not given any additional insulin injection before delivery. Hypoglycemia developed in two of these infants at 1 h and in the remaining 5 at 3 h. In all babies, hypoglycemia was asymptomatic and was treated with early oral feeding. The mean blood glucose levels measured by the glucometer and by the hospital laboratory were 24 ± 3 and 32 ± 4 mg/dL, respectively, in hypoglycemic babies. In babies who remained normoglycemic, the mean glucometer reading was 46 ± 4 mg. Respiratory distress developed in two neonates from group 1 and required constant airway positive pressure breathing. No neonatal deaths occurred. No statistical differences were noted either in maternal or neonatal blood pH, $\mathrm{Po_2}$, $\mathrm{Pco_2}$, or base excess at delivery (Table 3).

Maternal and Neonatal Blood Glucose Levels

In group 1, the mean maternal capillary and venous blood glucose levels at delivery were 101 ± 5 and 127 ± 12 mg/dL, respectively ($P = 0.05$). At delivery, the mean neonatal capillary blood glucose level (46 ± 3 mg/dL) was significantly lower than both the umbilical venous (135 ± 12 mg/dL) and arterial (103 ± 8 mg/dL) blood glucose levels in diabetic patients (group 1, $P = 0.01$) (Figure 1). The maternal venous blood glucose levels were greatest in the healthy patients given glucose before epidural anesthesia (group 2) and least in the healthy patients given lactated Ringer's solution infusion (group 3). In the neonatal umbilical venous blood of both group 1 and 2 patients, glucose levels were significantly greater compared with those of group 3 patients. The umbilical arterial blood of group 1 patients contained significantly greater glucose concentration than that of group 3 patients. (For P values, see Table 4.) The maternal venous blood glucose levels were significantly higher than the corresponding neonatal umbilical venous blood glucose levels in groups 2 ($P = 0.008$) and 3 ($P = 0.05$) but insignificantly lower than the corresponding neonatal umbilical venous blood levels in group 1.

Table 3. Maternal and Neonatal Blood Oxygen and Carbon Dioxide Tensions and Base Excess

	Po_2 (mm Hg)	Pco_2 (mm Hg)	pH	BE (mmol/L)
Maternal artery				
Group 1	230	29	7.44	−5.0
(diabetic)	(7)	(1)	(0.1)	(0.3)
Group 2	242	28.0	7.43	−5.2
(hyperglycemic)	(13)	(0.8)	(0.01)	(0.06)
Group 3	238	29	7.42	−6.0
(normoglycemic)	(7)	(1)	(0.1)	(0.3)
Umbilical vein				
Group 1	29	43	7.36	−1.0
	(2)	(2)	(0.01)	(0.4)
Group 2	31.9	39.0	7.35	−3.6
	(2.7)	(1.3)	(0.01)	(0.35)
Group 3	32	40	7.35	−3.5
	(1)	(2)	(0.01)	(0.3)
Umbilical artery				
Group 1	21	50	7.32	−1.0
	(3)	(3.5)	(0.02)	(0.6)
Group 2	17.0	50.0	7.29	−2.2
	(0.2)	(1.5)	(0.01)	(1.4)
Group 3	20	48	7.3	−3.0
	(1)	(2)	(0.01)	(0.3)

Po_2, oxygen tension; Pco_2, carbon dioxide tension; BE, base excess.
Data are mean ± 1 SE of 20 observations in group 1 and 15 each in groups 2 and 3. Figures within parentheses represent 1 SE.

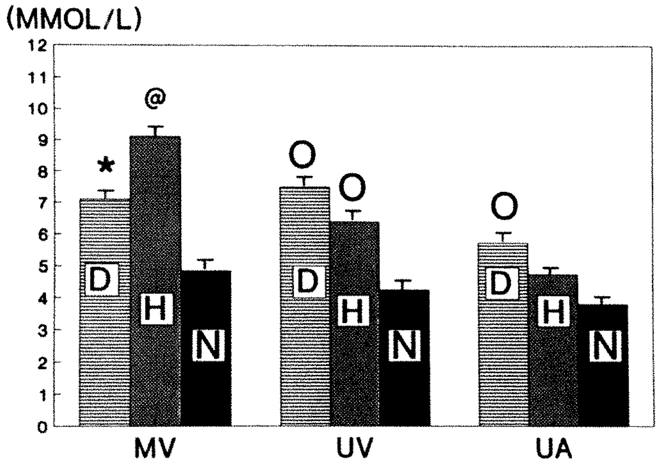

Figure 1. Maternal and neonatal blood glucose values at delivery. MV, maternal vein; UV, umbilical vein; UA, umbilical artery; D, diabetes (group 1); H, hyperglycemia (group 2); N, normoglycemia (group 3). *, Significantly different from groups 2 and 3. @, Different from groups 1 and 3. O, Different from group 3. For *P* values, see Table 4.

Table 4. *P* Values for Intergroup Comparisons

Substance	Blood sample	Groups 1 vs 2	Groups 1 vs 3	Groups 2 vs 3
Glucose	MV	0.02	0.008	0.00004
	UV	0.16	0.0003	0.008
	UA	0.08	0.002	0.09
Lactate	MV	0.021	0.007	0.68
	UV	0.004	0.5	0.0007
	UA	0.57	0.188	0.47
Pyruvate	MV	0.0005	0.167	0.013
	UV	0.0001	0.05	0.006
	UA	0.00004	0.04	0.003
Excess lactate	MV	0.001	0.05	0.11
	UV	0.82	0.016	0.026
	UA	0.69	0.167	0.77
Lactate/pyruvate ratio	MV	0.001	0.05	0.11
	UV	0.02	0.015	0.87
	UA	0.0033	0.003	0.94

MV, maternal vein; UA, neonatal umbilical artery; UV, neonatal umbilical vein.
Statistical analysis was done using analysis of variance. Intergroup comparisons were made using protected least significant difference method.

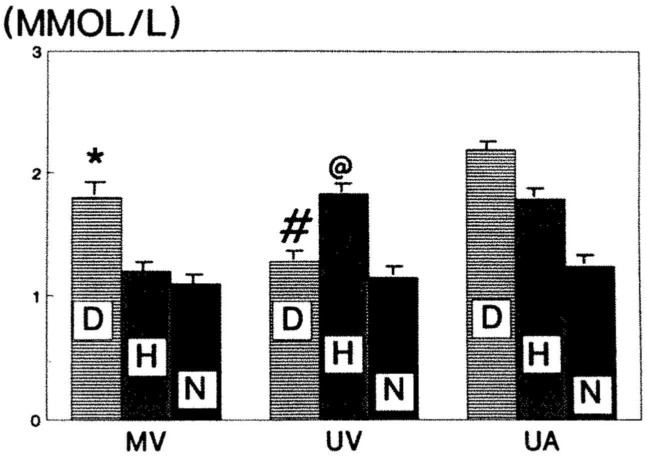

Figure 2. Maternal and neonatal blood lactate values. *, Significantly different from groups 2 and 3. #, Significantly different from group 2. @, Significantly different from groups 1 and 3. For abbreviations, see legend for Figure 1. For *P* values, see Table 4.

Blood Lactate

The maternal venous blood of group 1 patients contained more lactate than did that of either group 2 or group 3 patients. Neonatal umbilical venous blood in group 2 patients contained significantly more lactate than the corresponding samples from either group 1 or 3 with no differences in umbilical arterial blood lactate among the groups (Figure 2). (For *P* values, please see Table 4.)

Blood Pyruvate

The pyruvate levels in maternal venous blood were significantly lower in group 1 patients than in group 2 patients and significantly greater in group 2 compared with that in the other two groups. Both the

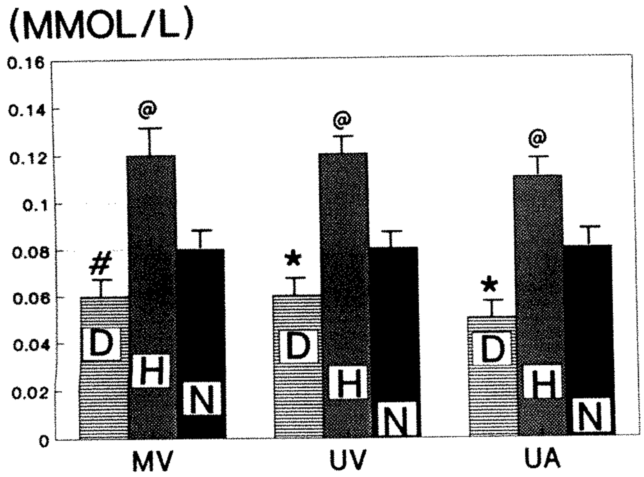

Figure 3. Maternal and neonatal blood pyruvate values. #, Significantly different from group 2. @, Significantly different from groups 1 and 3. *, Significantly different from groups 2 and 3. For abbreviations, see legend for Figure 1. For *P* values, see Table 4.

umbilical venous and arterial blood pyruvate levels in group 1 patients were significantly lower than the corresponding levels in the other two groups (Figure 3). (For *P* values, please see Table 4.) The blood pyruvate levels in both umbilical vein and artery were greatest in group 2.

Blood Excess Lactate and Lactate/Pyruvate Ratio

In maternal venous blood, excess lactate was significantly greater in group 1 compared with that in the other two groups. Both groups 1 and 2 had greater concentrations of excess lactate in the neonatal umbilical venous blood than did group 3, with no significant differences in the umbilical arterial blood values (Figure 4). In the maternal venous and neonatal umbilical venous and arterial blood, the lactate/pyruvate ratio was significantly greater in group 1 than in the other two groups (Figure 5). (For *P* values, please see Table 4.)

Discussion

Our data show that epidural anesthesia for cesarean section in diabetic women is associated with satisfactory neonatal Apgar scores and acid-base status at the time of birth. Our data also show that in diabetic parturients, neonatal hypoglycemia occurs more frequently and glucose homeostasis and glycolysis are altered. Maternal diabetes is associated with 21%–31% of neonatal hypoglycemia (12). The high incidence of hypoglycemia is probably due to hypertrophy of the β-cells of the neonate as well as to exaggerated secretory response of those cells to a given glucose load (5).

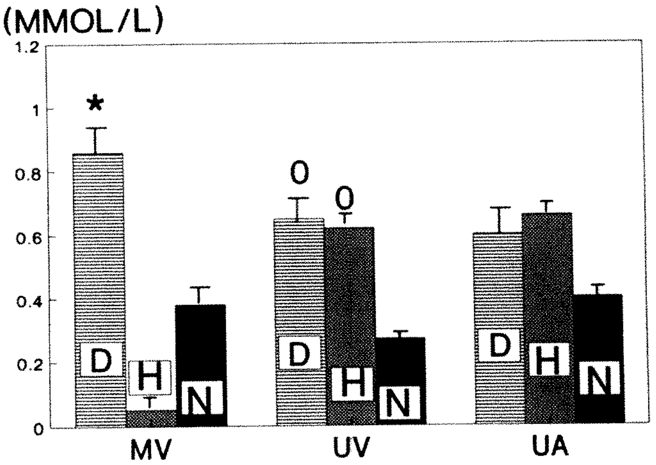

Figure 4. Maternal and neonatal blood excess lactate values. *, Different from groups 1 and 3. ○, Different from group 3. For abbreviations, see legend for Figure 1. For *P* values, see Table 4.

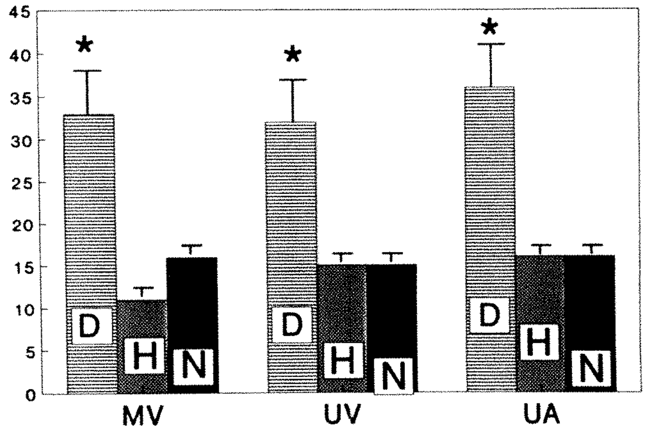

Figure 5. Maternal and neonatal blood lactate/pyruvate ratio. *, Significantly different from groups 2 and 3. For abbreviations, see legend for Figure 1. For *P* values, see Table 4.

As the incidence of neonatal hypoglycemia was significantly greater in the diabetic group than in the hyperglycemic group, the diabetic state seems to further increase the risk for neonatal hypoglycemia. Maternal hyperglycemia in group 2, however, was only moderate in our study and was induced by infusion of glucose at a rate of 20 g/h. Grylack et al. (13) found that both the rate and total amount of glucose administered to the mother are critical determinants of neonatal hypoglycemia and that when maternal glucose infusion rate does not exceed 20 g/h, the incidence of neonatal hypoglycemia is minimal.

Our data show that the maternal capillary blood glucose level was approximately 25% lower than the venous glucose level measured by the hexokinase method. The hexokinase method has been extensively investigated in the United States as a national glucose reference method (7,8). The reason for the discrepancy between the two methods may be owing to the following factors: (a) different sites of blood sampling, (b) the reflectance glucometers yield lower values than do enzymatic measurements especially at blood glucose concentrations less than 180 mg/dL (14), and (c) errors in glucometer calibration and sampling technique (15). As the glucometer measurements in our study were made by a well-trained nurse, the technical errors were probably minimal.

The increased umbilical venous glucose concentration in groups 1 and 2 at birth was due to maternal hyperglycemia. Although the glucose/insulin infusion in the diabetic patients appeared to maintain a reasonable maternal venous blood glucose concentration, it perhaps failed to prevent fetal hyperglycemia as evidenced by the high neonatal umbilical venous blood glucose level at delivery. The umbilical venous blood glucose concentration is usually lower than the maternal venous blood concentration with maternal euglycemia or iatrogenic hyperglycemia (7,16,17), which was also the case in this study (Figure 1). However, in the diabetic group, the umbilical venous blood glucose level tended to be higher than the maternal venous blood glucose level. Two factors may have been responsible for this: (1) the supplemental insulin injections to the mother might have acutely reduced maternal venous glucose with neonatal glucose level lagging behind the maternal glucose level, and (b) there may have been inadequate metabolic control by the glucose/insulin infusion regimen. Feldberg et al. (18) have reported less effective metabolic and blood glucose control during labor in diabetic women receiving glucose/insulin infusion compared with that in those maintained by continuous subcutaneous insulin infusion. In their study, the mean intrapartum maternal venous blood glucose level was 127 mg/dL (similar to our values) in women receiving glucose/insulin infusion and 90 mg/dL in those given continuous subcutaneous insulin infusion. Thus, glucose/insulin therapy, in conjunction with insulin bolus injections to maintain near normal capillary glucose measurement on the day of operation, appears less effective in achieving neonatal normoglycemia. Our data show that the presence of neonatal umbilical venous or arterial blood hyperglycemia (which determine neonatal β-cell response) cannot be predicted by neonatal capillary glucose measurement at the time of delivery. As we did not study other modes of peripartal insulin administration, we do not know how effective other insulin regimens might have been with respect to neonatal hyperglycemia.

Because of increased placental glycolysis, maternal hyperglycemia results in increased neonatal umbilical venous lactate and pyruvate concentrations in nondiabetic patients (4,7). The decreased lactate and pyruvate concentrations in the neonatal umbilical venous blood in the diabetic group probably signify diminished glycolysis in the placenta as a result of chronic lack of insulin and/or alterations in the placental enzymes of glycolysis and gluconeogenesis. Diamant et al. (19) reported an overall reduction in glycolytic flow in isolated human diabetic placentas. A diabetic state is associated with reduced activity of glucokinase and phosphofructokinase, two important regulatory enzymes in the glycolytic pathway (20). Glucokinase converts α-D-glucose to α-D-glucose 6-phosphate, and phosphofructokinase converts D-fructose-6-phosphate to D-fructose 1-6 diphosphate (21). Reduced glycolysis in diabetic patients is attributed to increased fatty acid oxidation, increased levels of certain amino acids, and/or uteroplacental insufficiency (19). A diabetic state also increases placental fat content and augments maternal-fetal fat transfer (22). Similar factors are believed to inhibit skeletal muscle glycolysis in animals with experimentally induced diabetes (23).

A consistent finding in our study with respect to glycolysis is the highly significant reduction in blood pyruvate concentration in the maternal and neonatal blood. The reduction may be due to a general decrease in the glycolytic flow in the maternal and fetal tissues in the diabetic patients (19) or more specifically to reduced activity of pyruvate kinase, which converts phosphoenolpyruvate to pyruvate (19,21). Daimant et al. has shown that pyruvate kinase activity was significantly reduced in placentas from diabetic women. Singh and Feigelson (24) have shown reduced activities of pyruvate kinase, hexokinase, and phosphofructokinase in the lungs of offspring of rats with streptozotocin-induced diabetes. The diminished glycolytic capacity, together with altered glycogen metabolism in the lungs, is believed to be associated with decreased synthesis of surfactant and with increased incidence of respiratory distress in the newborn of diabetic patients (24). Increased fatty acid oxidation in the mother and fetus may also be responsible for the reduced pyruvate kinase activity (19).

Increased lactate/pyruvate ratio in neonatal blood with only minor changes in excess lactate in the diabetic group is mainly due to the reduced pyruvate level and not to the increased lactate levels. As neither the maternal and neonatal blood pH nor the base excess differed among the groups, the increased lactate/pyruvate ratio does not signify the presence of lactic acidosis.

In summary, epidural anesthesia for elective cesarean section in diabetic patients receiving glucose/insulin infusion was associated with normal neonatal

Apgar scores and acid-base status. Maternal and neonatal metabolic abnormalities including hyperglycemia and reduced blood pyruvate level were noted to occur at delivery with no evidence of neonatal lactic acidosis. Postpartum hypoglycemia developed in a significant number of neonates.

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Effect of Intravenously Administered Dexmedetomidine on Pain After Laparoscopic Tubal Ligation

Martina S. Aho, MD, Olli A. Erkola, MD, PhD, Harry Scheinin, MD, PhD,
Ann-Mari Lehtinen, MD, PhD, and Kari T. Korttila, MD, PhD

Department of Anesthesia, Women's Hospital, Helsinki University Central Hospital, Helsinki, Finland; Orion Corporation Farmos, Research Center, Turku, Finland

Ninety-six women undergoing laparoscopic tubal ligation were randomized to receive intravenously either 0.2 or 0.4 μg/kg of dexmedetomidine, 60 μg/kg of oxycodone, or 250 μg/kg of diclofenac for postoperative pain in a double-blind study design. The study drugs were administered in the recovery room for moderate or severe pain and were repeated until pain subsided or disappeared. In the group receiving diclofenac, 83% of the patients required analgesic supplementation with morphine. This contrasted ($P < 0.01$) with 33% of the patients receiving either oxycodone or the higher dose of dexmedetomidine. After the first dose of oxycodone was injected, the visual analogue scale for pain (0%–100%) was reduced from 58% to 33%, whereas corresponding pain relief was only achieved after the third injection of 0.4 μg/kg of dexmedetomidine. Repeated doses of 0.2 μg/kg of diclofenac or dexmedetomidine did not reduce the visual analogue scale value by more than 17%. More sedation was seen with the higher dose of dexmedetomidine than with either diclofenac or oxycodone ($P < 0.001$). Both doses of dexmedetomidine decreased heart rate when compared with diclofenac ($P < 0.001$). In the group given 0.4 μg/kg of dexmedetomidine, 33% of the patients required atropine for bradycardia. The authors conclude that after laparoscopic tubal ligation, intravenously administered dexmedetomidine relieves pain and reduces opioid drug requirement but is attended by sedation and a high incidence of bradycardia.

(Anesth Analg 1991;73:112–8)

Several recent studies have demonstrated the beneficial effects of the perioperative administration of α_2-adrenoceptor agonists in anesthesiology (1–3). Clonidine has been shown to attenuate hemodynamic responses during laryngoscopy and endotracheal intubation (2,3) and to reduce the dose requirements of inhaled anesthetics (4–8). In many experimental animal models, clonidine is a potent analgesic, which may also potentiate morphine analgesia (9–12). After intrathecal injection, clonidine is between 10 and 20 times more potent than morphine in relieving pain (13). In surgical patients, clonidine has analgesic properties after its systemic administration (14,15).

Dexmedetomidine, the pharmacologically active *d*-isomer of medetomidine (4,(5)-[1-(2,3-dimethylphenyl)ethyl]imidazole) is a highly specific and selective α_2-adrenoceptor agonist (16,17). Medetomidine shows full agonism at α_2-adrenoceptor (17) and its α_2/α_1-binding selectivity ratio is 1620:1 compared with 220:1 for clonidine (18). The racemic composition of medetomidine induces anesthesia in dogs (19–21). In humans, dexmedetomidine has exhibited sedative properties and is well tolerated (22). It causes a dose-dependent decrease in blood pressure and heart rate, and it also decreases the level of norepinephrine in plasma (22). A single intravenous bolus of dexmedetomidine given 15 min before the induction of anesthesia decreased thiopental requirements during cervical dilatation and uterine curettage (23), attenuated the hemodynamic responses to laryngoscopy and endotracheal intubation, and diminished isoflurane requirements during abdominal hysterectomy (24).

In the present study, we determined whether dexmedetomidine at two different doses alleviates visceral pain after laparoscopic tubal ligation. For comparison, comparable groups of patients were treated with intravenous diclofenac or oxycodone. Diclofenac is a short-acting nonsteroidal antiinflammatory agent and oxycodone is a narcotic analgesic similar to morphine.

Accepted for publication April 23, 1991.

Address correspondence to Dr. Aho, Department of Anesthesia, Women's Hospital, Helsinki University Central Hospital, Haartmaninkatu 2, SF-00290 Helsinki, Finland.

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0003-2999/91/$3.50

Table 1. Characteristics of Patients and Their Blood Pressure and Heart Rate Values Before Induction of Anesthesia

	Diclofenac (250 μg/kg)	Oxycodone (60 μg/kg)	Dexmedetomidine	
			0.2 μg/kg	0.4 μg/kg
No of patients	24	24	24	24
Age (yr)	39 ± 4	39 ± 4	40 ± 3	37 ± 4
Weight (kg)	64 ± 9	64 ± 10	62 ± 7	63 ± 8
Height (cm)	164 ± 5	164 ± 4	164 ± 6	166 ± 5
Heart rate (beats/min)	71 ± 8	72 ± 8	72 ± 7	73 ± 14
SBP (mm Hg)	121 ± 15	114 ± 12	118 ± 17	116 ± 13
DBP (mm Hg)	76 ± 8	70 ± 14	74 ± 11	73 ± 10

SBP, systolic blood pressure; DBP, diastolic blood pressure.
Values are mean ± SD. No statistically significant differences are present.

Methods

The study protocol was approved by the Women's Hospital Ethical Committee and by the Finnish National Board of Health. Written informed consent was obtained from each patient. The study population was composed of 96 women, aged 30–46 yr, undergoing laparoscopic tubal ligation by the Filshie method. The patients were healthy, normotensive ASA I women receiving no medications. The patients' demographic characteristics are shown in Table 1.

A double-blind study design was used with the patients randomized into four groups, each containing 24 patients. On the day of operation, premedication consisted of 0.1 mg/kg of diazepam given orally 45–60 min before the induction of anesthesia. On the patients' arrival in the operating room, electrocardiographic monitoring (lead II) and automatic noninvasive blood pressure measurement were started.

General Anesthesia

Before induction of anesthesia, each patient intravenously received 0.2 mg of glycopyrrolate and 0.6 mg of vecuronium bromide. Anesthesia was then induced with 2 mg/kg of propofol, and succinylcholine was given to facilitate laryngoscopy and endotracheal intubation. Each patient then received isoflurane (0.3% end-tidal concentration) in 70% nitrous oxide and 30% oxygen. After the succinylcholine-induced neuromuscular blockade had dissipated, vecuronium bromide was titrated to achieve and maintain 80% twitch inhibition as assessed with a nerve stimulator (25). No opiate narcotics were administered during the operation. At the end of anesthesia, neuromuscular blockade was antagonized with 2 mg of neostigmine and 0.4 mg of glycopyrrolate.

Study Outline

After laparoscopy, the study drug was administered as an intravenous bolus dose for postoperative pain in the postanesthesia care unit whenever the patient suffered moderate to severe pain. The patients received a coded solution containing either 0.2 or 0.4 μg/kg of dexmedetomidine hydrochloride (Orion Corporation Farmos, Turku, Finland), 60 μg/kg of oxycodone chloride (Oxanest, Leiras, Helsinki, Finland), or 250 μg/kg of diclofenac (Voltaren, Ciba-Geigy, Basel, Switzerland). The double-blind design was maintained by an independent nurse who prepared drug solutions in coded syringes. The study drug was given at no less than 5-min intervals until pain had subsided. No more than three consecutive doses of analgesic study drug were given during 1 h or a total of five doses during the 2-h follow-up. If adequate analgesia was not achieved with the test drugs, morphine was administered at a dose of 0.06 mg/kg and was repeated if necessary. Once treated with morphine, the patient did not receive additional doses of the trial drugs and subsequently was excluded from the study. Droperidol (10 μg/kg) was given intravenously for emesis when needed, and 0.4 mg of atropine for bradycardia (as defined by a decrease in heart rate to below 40 beats/min).

Variables Studied

1. The relief of postoperative pain was estimated by the patient herself. When the patient rated her pain to be moderate or severe, scoring with the visual analogue scale (VAS) was initiated. The VAS consists of a 50-cm-long horizontal bar on which the left end (0%) denotes a pain-free state and the right end (100%) denotes intolerable pain. The patient indicates the amount of pain experienced by drawing a vertical line on the bar (26). The VAS was used before administration of each trial drug and at 5-min intervals after drug administration for 20 min and then at 10-min intervals until another study drug dose was administered or until the end of the study period.
2. The number of patients who needed morphine was recorded. If adequate postoperative analgesia was not achieved with the three consecutive doses

Table 2. Visual Analogue Scale Before and After Drug Treatment

	Diclofenac (250 μg/kg)	Oxycodone (60 μg/kg)	Dexmedetomidine		Statistics
			0.2 μg/kg	0.4 μg/kg	
VAS before study drug (%)	56 ± 12	58 ± 18	57 ± 13	61 ± 16	F(3,92) = 0.6, $P = 0.598$
ΔVAS after[a]					
1st drug (%)	5 ± 15 (24)	25 ± 15[d] (24)	9 ± 15 (24)	11 ± 14 (24)	Interaction drug × time F(6,256) = 2.6, $P = 0.017$
2nd drug (%)	8 ± 14 (24)	23 ± 19[d] (20)	9 ± 14 (24)	19 ± 18 (24)	Drug main effect F(3,256) = 8.0, $P < 0.001$
3rd drug (%)	3 ± 14 (22)	24 ± 18[d] (17)	17 ± 17[e] (23)	21 ± 14[d] (21)	
Patients requiring morphine (%)[b]	83	33[d]	71	33[d]	$G^2(3) = 20.3$, $P < 0.001$
Patients shivering (%)[c]	42	4[e]	17	4[e]	$G^2(3) = 15.7$, $P = 0.001$

F, one-way analysis of variance; G^2, likelihood ratio χ^2-test. Values are mean ± SD and percent.

[a] Change in VAS score (0% = no pain, 100% = intolerable pain). After the ΔVAS value is the number of patients who required and received the injection.

[b] Patients who required administration of morphine during recovery.

[c] Patients who suffered from postoperative shivering after receiving study drug but before morphine treatment.

[d] $P < 0.1$ versus diclofenac.

[e] $P < 0.05$ versus diclofenac.

of study drug during 1 h or with a total of five doses during the 2-h follow-up, morphine was administered for pain control. Morphine was administered until the patient was satisfied and did not require additional doses of analgesic.

3. The time to morphine administration was determined as the time elapsed from the first dose of study drug until morphine treatment was needed (e.g., the fourth injection of analgesic during the first hour of recovery or the sixth injection of analgesic during the whole study session).
4. Postoperative shivering, if present, was recorded at the same time as the intensity of pain as "yes" or "no."
5. Sedation scores (1 = awake, eyes open; 2 = asleep, easy to arouse; 3 = asleep, difficult to arouse; 4 = asleep, not arousable) were estimated at the same time as the intensity of the pain.
6. Blood pressure and heart rate were recorded on the left arm with a noninvasive, automated blood pressure monitor (Datascope Accutorr, Datascope Corp., Japan). The measurements were performed at 1-min intervals for the first 10 min after each dose of the study drug and at 5-min intervals after that.
7. Respiratory rate and oxygen saturation from the finger (pulse oximeter) were recorded during the immediate postoperative period at 5-min intervals.

Statistical Analysis

The statistical analysis for demographic data and single efficacy end points was performed with one-way analysis of variance; Bonferroni-corrected contrasts were used in pairwise comparisons. Frequency data were compared with the likelihood ratio χ^2-test using the variable estimates (cross-product ratios) in assessing the differences from the diclofenac group. Sedation scores were analyzed with nonparametric Kruskall-Wallis one-way analysis of variance using the Bonferroni-corrected Mann-Whitney test for pairwise comparisons. The time to first morphine dosage was compared with the log-rank test. Changes in VAS scores were analyzed using general mixed-model analysis of covariance, the value before injection being taken as the covariate. A P value of less than 0.05 was considered statistically significant. The analyses were performed with BMDP software (BMDP, Statistical Software, Los Angeles, Calif.).

Results

The patient groups were similar with respect to age, weight, height, and heart rate and blood pressure values before induction of anesthesia. Demographic characteristics of the patients are shown in Table 1.

Antinociceptive Effect

The VAS values did not differ among the groups before the first administration of the study drug (Table 2). Patterns of pain relief differed between the treatment groups after the administration of the study drugs. Substantial pain relief by VAS was achieved after the first dose of oxycodone was given, with a reduction of the VAS value from 58% to 33%. This degree of pain relief was reached after the third administration of 0.4 μg/kg of dexmedetomidine. Similar maximal reduction of VAS scores was achieved after a third administration of either oxycodone (24%) or the higher dexmedetomidine dose of 0.4 μg/kg (21%) (Table 2).

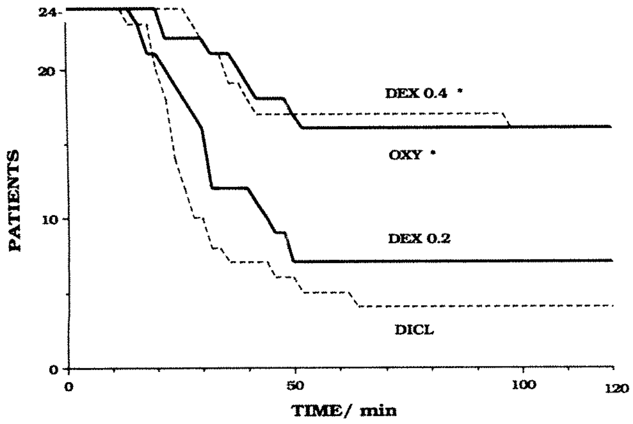

Figure 1. Number of patients in various study groups with satisfactory analgesia without need to switch to morphine after arrival in the recovery room. Time 0 min = arrival in recovery room. Dexmedetomidine (0.4 μg/kg) (DEX 0.4) and oxycodone (60 μg/kg) (OXY) differ significantly from dexmedetomidine (0.2 μg/kg) (DEX 0.2) and from diclofenac (250 μg/kg) (DICL). Time to administration of first morphine dose compared with log-rank test. *$P < 0.001$ between study groups.

In the diclofenac group, 20 of the 24 (83%) patients required supplemental doses of morphine, whereas only 8 patients (33%) in each of the groups receiving either oxycodone or the higher dose of dexmedetomidine had analgesia supplemented with morphine ($P < 0.005$). The median duration time before supplementation with morphine was 32 min (95% confidence interval, 30–45 min) for the low-dose dexmedetomidine (0.2 μg/kg) group and 25 min (23–32 min) for the diclofenac group. The time patterns of the high-dose dexmedetomidine (0.4 μg/kg) and oxycodone groups were similar; median times and confidence intervals could not, however, be assessed owing to the fact that less than 50% of patients in both groups needed morphine. As seen in Figure 1, the patients receiving diclofenac or the lower dose of dexmedetomidine required morphine significantly sooner ($P < 0.001$) than did patients receiving oxycodone or the higher dose of dexmedetomidine.

In the diclofenac group, 10 of 24 patients (42%) suffered from shivering before morphine supplement. This contrasted ($P < 0.05$) with only 1 patient (4%) in the high-dose dexmedetomidine and oxycodone groups. Thus, 0.4 μg/kg of dexmedetomidine prevented postoperative shivering as effectively as did oxycodone (Table 2).

Sedation

On arrival in the recovery room, all patients were either awake or easily arousable. Before the need of morphine, three patients in the high-dose dexmedetomidine group were not arousable, and 10 others were difficult to arouse (reacting only to loud voice or shaking). This contrasted clearly ($P < 0.001$) with the diclofenac and oxycodone groups, in which all the patients were awake or easily arousable. In the low-dose dexmedetomidine group, only 1 of the 24 patients was difficult to arouse. Also in the oxycodone group, patients were more sedated (lying eyes closed) than in the diclofenac group ($P < 0.05$) (Table 3). The number of heavily sedated patients (difficult to arouse or not arousable) did not increase in any study group after morphine administration.

Respiratory Variables

On arrival at the recovery room, oxygen saturation and respiratory rate did not differ among the study groups. Before the administration of morphine, the minimum respiratory rate differed between the groups ($P < 0.05$), being lowest in the oxycodone group (12 breaths/min). The minimum respiratory frequency per minute was significantly higher ($P < 0.05$) in patients receiving 0.4 μg/kg of dexmedetomidine (14 breaths/min) than that in those receiving oxycodone. Oxycodone administration resulted in a significantly greater decrease in oxygen saturation than did the low or high doses of dexmedetomidine ($P < 0.001$). The effect of dexmedetomidine in oxygen saturation did not differ from that of diclofenac (Table 3).

Hemodynamic Variables

On arrival at the recovery room, heart rate and blood pressure values did not differ among the groups (Table 4). Repeated injections of both doses of dexmedetomidine decreased heart rate more than oxycodone or diclofenac did ($P < 0.001$). Between the two doses of dexmedetomidine, 0.2 and 0.4 μg/kg, a clear dose-response effect was noticed ($P = 0.01$). Eight patients (33%) in the high-dose dexmedetomidine group needed atropine for bradycardia. In seven of the eight patients, bradycardia occurred after the injections of 0.4 μg/kg of dexmedetomidine but before the possible administration of morphine. Two patients required 0.4 mg of atropine twice; but in all others, bradycardia improved immediately after the first administration. No other electrocardiographic changes besides sinus bradycardia were observed. No patients in the other groups required atropine. During the study, blood pressure values did not differ significantly among the groups (Table 4).

Discussion

The prototype α_2-agonist clonidine has been shown to possess clear analgesic properties in animal models

Table 3. Respiratory Variables

	Diclofenac (250 μg/kg)	Oxycodone (60 μg/kg)	Dexmedetomidine 0.2 μg/kg	Dexmedetomidine 0.4 μg/kg	Statistics
Patients sedated (%)^{a}	38	88^{d}	88^{d}	100^{f}	$X^2_K(3) = 44.9$, $P < 0.001$
Respiratory rate (breaths/min)					
Baseline^{b}	17 ± 5	15 ± 3	17 ± 5	18 ± 5	F(3,92) = 1.5, $P = 0.208$
Minimum^{c}	15 ± 4	12 ± 2^{e}	13 ± 3	14 ± 3	F(3,92) = 3.8, $P = 0.012$
Oxygen saturation (%)					
Baseline^{b}	99 ± 1	98 ± 2	99 ± 1	98 ± 2	F(3,92) = 1.2, $P = 0.308$
Minimum^{c}	98 ± 1	95 ± 1^{f}	97 ± 1	97 ± 1	F(3,92) = 9.9, $P < 0.001$

X^2_K, Kruskall-Wallis one-way analysis of variance; F, one-way analysis of variance.
Values are mean ± SD or percent.
[a] Patients lying with eyes closed (easy or difficult to arouse or not arousable) before morphine treatment.
[b] Noted on arrival in the recovery room.
[c] Obtained after injection of study drugs but before administration of morphine.
[d] $P < 0.05$ versus diclofenac.
[e] $P < 0.01$ versus diclofenac.
[f] $P < 0.001$ versus diclofenac.

Table 4. Hemodynamic Variables

	Diclofenac (250 μg/kg)	Oxycodone (60 μg/kg)	Dexmedetomidine 0.2 μg/kg	Dexmedetomidine 0.4 μg/kg	Statistics
Systolic blood pressure (mm Hg)					
Baseline^{a}	125 ± 16	121 ± 16	133 ± 25	131 ± 17	F(3,92) = 1.8, $P = 0.148$
Minimum^{b}	100 ± 13	99 ± 13	95 ± 14	94 ± 11	F(3,92) = 1.2, $P = 0.305$
Diastolic blood pressure (mm Hg)					
Baseline^{a}	74 ± 11	68 ± 14	75 ± 18	71 ± 13	F(3,92) = 0.8, $P = 0.496$
Minimum^{b}	52 ± 11	50 ± 8	46 ± 14	46 ± 8	F(3,92) = 1.7, $P = 0.171$
Heart rate (beats/min)					
Baseline^{a}	66 ± 12	67 ± 11	66 ± 14	67 ± 15	F(3,92) = 0.04, $P = 0.987$
Minimum^{b}	55 ± 7	53 ± 5	50 ± 8^{d}	44 ± 8^{e}	F(3,92) = 11.3, $P < 0.001$
Patients requiring atropine^{c} (%)	0	0	0	33^{e}	$G^2(3) = 24.5$, $P < 0.001$

F, one-way analysis of variance; G^2, likelihood ratio χ^2-test.
Values are mean ± SD or percent.
[a] Obtained on arrival in the recovery room.
[b] Obtained after administration of study drug but before administration of morphine.
[c] Atropine administered if heart rate <40 beats/min.
[d] $P < 0.05$ versus diclofenac.
[e] $P < 0.001$ versus diclofenac.

(9–12), but few controlled studies have been published on the analgesic efficacy of clonidine in surgical patients after parenteral administration. The principal results of our study indicated that the intravenously administered, novel and highly selective α_2-adrenoceptor agonist dexmedetomidine provides analgesia for visceral pain after laparoscopic tubal ligation.

Generally, pain after tubal ligation has not been used as a model to study new analgesics. We chose this model because laparoscopy and application of tubal clips are easy to standardize and because they produce moderate to severe pain usually requiring treatment in all patients. Furthermore, to validate the possible analgesic efficacy of dexmedetomidine, a mild analgesic (a small dose of diclofenac) and a potent opiate analgesic (oxycodone) were used as control agents.

When administered intrathecally or epidurally, clonidine has been reported to produce profound analgesia without respiratory depression (27). In the postoperative setting, the usefulness of epidural clonidine, administered as an intravenous bolus dose, may be limited by hemodynamic depression or by a short duration of analgesia (28). In contrast, epidural clonidine infusion offers effective analgesia without markedly decreasing blood pressure in patients with severe intractable chronic cancer pain (29). When clonidine is supplemented with either a local anesthetic (30) or with a narcotic (31), the antinociceptive effect is prolonged. Complete pain relief in a patient with intractable cancer pain was achieved with intrathecal clonidine alone (32).

Unlike clonidine, which is a partial α_2-adrenoceptor agonist (17), medetomidine may provide an interesting profile with regard to analgesia. The racemic composition of medetomidine has a dose-dependent analgesic effect in various animal models (33,34), and according to Segal et al. (35), the *d*-isomer of medetomidine prolonged the latency of the behavioral response to tail clamping in rats under halothane anesthesia. This analgesic effect of dexmedetomidine could be reversed by idazoxan, an α_2-adrenoceptor antagonist, but not by an opiate antagonist.

In a recent study with human volunteers, medetomidine produced a significant attenuation of the affective-motional component (unpleasantness) of tourniquet-induced ischemic pain, whereas the sensory-discriminative component (pain-magnitude estimate) of the ischemic pain was not attenuated (36). The possible site of action for antinociception produced by clonidinelike drugs has been identified to be both spinal and central (12,37,38). Peripheral antinociception by an α_2-adrenoceptor-mediated local release of encephalinlike substances is also possible (39).

In our study, dexmedetomidine had analgesic properties and reduced morphine requirements but was accompanied by marked sedation, some patients being difficult to arouse. Since the subjective component of the ischemic tubal pain was reduced as measured by lowered VAS values, this may reflect the sedative properties of dexmedetomidine as well as a specific antinociceptive effect.

Although the patients treated with 0.4 μg/kg of dexmedetomidine were more sedated than the patients in the oxycodone group, respiratory rate and oxygen saturation were higher in the dexmedetomidine group. This leads us to postulate that by using dexmedetomidine as an adjuvant to antinociception, it may be possible to reduce the amount of opiate narcotics needed for analgesia and to avoid some side effects of opioid treatment (such as respiratory depression).

A consistent effect of dexmedetomidine therapy is the development of bradycardia (22). Therefore, all the patients studied received glycopyrrolate during induction and at the end of anesthesia when neuromuscular blockade was antagonized. Nevertheless, bradycardia, which rapidly responded to atropine without untoward effects, developed in eight patients in the high-dose dexmedetomidine group in contrast to 0 patients in all other groups.

It is concluded that although dexmedetomidine alleviated pain after laparoscopic tubal ligation, the drowsiness and bradycardia caused by the drug was not desirable during the recovery period. Further studies should be carried out to determine whether dexmedetomidine reduces opioid requirements, as clonidine has been shown to do (40), when administered earlier during operation and anesthesia.

We are grateful to Dr. Antero Kallio from Farmos for providing us with dexmedetomidine. We also thank Jouni Vuorinen, MSc, for skillfully performing statistical analyses and Kaarina Backas, nurse anesthetist, for taking excellent care of our patients.

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Effect of Prior Anesthetic Solution on Epidural Morphine Analgesia

James C. Eisenach, MD, Timothy J. Schlairet, DO, Christopher E. Dobson II, MD, and David H. Hood, MD

Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, North Carolina

The quality and duration of analgesia and incidence of side effects following epidurally administered morphine after cesarean section are highly variable. Two suggested sources of this variability are prior use of epinephrine-containing solutions, which may enhance both analgesia and side effects of morphine, and prior use of 2-chloroprocaine, which may inhibit epidural morphine analgesia. To examine these proposed sources of this variability we performed two studies. In the first, designed to test epinephrine's effect, 30 women underwent testing for epidural catheter tip location with injection of 2-chloroprocaine, followed by either 0.5% bupivacaine alone or 0.5% bupivacaine with 5 μg/mL epinephrine for epidural anesthesia. Inclusion of epinephrine with bupivacaine decreased the bupivacaine dose needed to achieve a T-4 sensory block by 24% ($P < 0.05$), but did not alter analgesic duration or the incidence of side effects of epidural morphine (5 mg). In the second study, designed to test the effect of 2-chloroprocaine, 30 women received 7 mL of either 2% 2-chloroprocaine or lidocaine for epidural catheter testing, followed by 0.5% bupivacaine for epidural anesthesia. Compared to lidocaine testing, 2-chloroprocaine decreased the duration of epidural morphine analgesia (median 16 h with 2-chloroprocaine vs 24 h with lidocaine; $P < 0.05$) without altering the incidence of side effects. The authors conclude that addition of epinephrine to local anesthetic does not increase the incidence of side effects or the analgesic effect from epidurally administered morphine. 2-Chloroprocaine, even when administered in small doses remote to the time of morphine injection, interferes with the duration of epidural morphine analgesia.

(Anesth Analg 1991;73:119–23)

Although epidurally administered morphine offers many advantages over other analgesic therapies after cesarean section (profound analgesia, minimal sedation, and opioid dose), its reported duration is quite variable. For example, the proportion of patients experiencing complete analgesia for 24 h after 5 mg of epidural morphine ranges from 50% (1) to 98% (2). Fear by anesthesiologists of delayed respiratory depression may lead to inadequate treatment of pain during this period. Choice of local anesthetic solution for intraoperative epidural anesthesia may alter the efficacy of subsequently administered morphine. For example, it has been suggested that prior use of epinephrine-containing solutions enhances epidural morphine analgesia (3). Addition of epinephrine to bupivacaine may further increase the high incidence of nausea, vomiting, and pruritus following epidurally administered morphine after cesarean section (3). However, there are no studies directly examining the analgesic efficacy and incidence of side effects of epidurally administered morphine after use of bupivacaine with and without epinephrine. Other work suggests that use of 2-chloroprocaine for intraoperative anesthesia inhibits epidural opioid analgesia (4). Epidurally administered fentanyl is ineffective when it is immediately preceded by even a small dose of 2-chloroprocaine to confirm catheter tip location (5). Whether epidurally administered morphine would be similarly affected by such a small dose of 2-chloroprocaine administered more than 1 h previously is unknown. This study examines the effects of addition of epinephrine and of using 2-chloroprocaine or lidocaine to confirm location of the catheter tip on the analgesic duration and incidence of side effects of epidurally administered morphine.

Methods

After approval by the Clinical Research Practices Committee and informed consent from the patients

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Presented in part at the Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Accepted for publication April 2, 1991.

Address correspondence to Dr. Eisenach, Department of Anesthesia, Wake Forest University Medical Center, 300 South Hawthorne Road, Winston-Salem, NC 27103.

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0003-2999/91/$3.50

Table 1. Treatment Groups

Study part	n	Local anesthetic Test doses	Local anesthetic Maintenance	Morphine bolus (mg)
1	11	2-CP	Bupivacaine	5
	17	2-CP	Bupivacaine + epinephrine	5
2	15	2-CP	Bupivacaine	5
	15	Lidocaine	Bupivacaine	5

2-CP, 2-chloroprocaine.

were obtained, 60 ASA physical status I or II women scheduled for cesarean section under epidural anesthesia were studied. All women had uncomplicated pregnancies and were taking no medications. After subcutaneous infiltration with 1% lidocaine, a single distal port catheter was inserted ≤3 cm into the epidural space via a No. 17 Touhy needle. Epidural catheter tip location was tested with 2% local anesthetic solution (2 mL followed in 5 min by 5 mL of lidocaine or 2-chloroprocaine), and epidural anesthesia was provided with 0.5% bupivacaine with or without 5 μg/mL of epinephrine according to study protocol (Table 1). Bupivacaine solutions were administered in 5-mL increments (15 mL over 10 min, then 5 mL every 20 min) to establish sensory blockade to pinprick to T-4. Additional injections of 5-mL bupivacaine solutions were administered intraoperatively as needed to maintain a T-4 sensory blockade to pinprick. Patients receiving >50 mL of local anesthetic or requiring intraoperative opioid analgesia were dropped from the study. Immediately after delivery, all patients received droperidol (0.5 mg IV) for postoperative nausea prophylaxis and 5 mg of preservative-free morphine in a 10-mL volume. The study was randomized and double-blind, and study parts 1 and 2 were performed sequentially.

In the recovery room, the level of sensory blockade to pinprick was assessed every 15 min until a two-segment regression had occurred. Parturients rated their level of pain using a five-point verbal scale (1 = comfortable, 2 = mildly uncomfortable, 3 = very uncomfortable, 4 = in pain, 5 = in bad pain) and nurses questioned them for the presence of nausea and pruritus every 2 h while awake for 24 h after surgery. Nurses assessed sedation using a five-point scale (1 = wide awake, 2 = drowsy, 3 = dozing intermittently, 4 = mostly sleeping, 5 = only awakens when aroused) and recorded respiratory rate every 2 h for 24 h after surgery. In addition, nurses monitored respiratory rate every hour for 24 h in all study patients. Age, height, weight, bupivacaine dose, and time, dose, and indication for all medications given during the study period were recorded. If no systemic opioids were administered for 24 h, the duration of epidural morphine analgesia was assigned to be 24 h.

Drugs

The following drugs were used in this study: bupivacaine, 2-chloroprocaine, and lidocaine (Astra Pharmaceuticals, Westborough, Mass.) and morphine sulfate (epidural: Elkins-Sinn, Cherry Hill, N.J.; intravenous: Wyeth Laboratories, Philadelphia, Pa.).

Statistical Analysis

Data are presented as mean ± SEM, except analgesia duration, which is presented as the median. Analgesia duration was defined as the time from epidural morphine injection until the first request for systemic analgesic medication. Pain and sedation scores after systemic analgesic administration were excluded from analysis. In accordance with previous studies of postoperative analgesia (1,6), pain and sedation scores obtained from 10 PM to 6 AM were excluded from analysis. Although the two study parts were similar in design, each part was analyzed separately. Continuous maternal demographic and bupivacaine dose data were compared within each part using a Student's t-test. Noncontinuous demographic data, pain and sedation scores, and incidence of side effects were compared within each part using χ^2 or Kruskal-Wallis analysis or Fisher-Yates exact test where appropriate. Duration of analgesia within each part was compared by the Kaplan-Meier method followed by the log rank test. $P < 0.05$ was considered significant.

Results

Two patients in the plain bupivacaine group of part 1 required systemic opioid supplementation during surgery and were dropped from the study. Within each part, the groups did not differ in demographic data (Table 2), nor did they differ in duration of surgery or incidence of sensory block more cephalad than T-4. The groups did not differ in time-course of side effects. Incidence of nausea peaked 4–6 h after epidural morphine injection, whereas incidence of pruritus exceeded 40% within 90 min of injection and remained >40% throughout the rest of the study period.

Part 1: Effect of Epinephrine

Addition of epinephrine decreased the bupivacaine dose needed to establish sensory blockade to T-4 as well as the total bupivacaine dose (Table 3, upper

Table 2. Patient Demographics

Group	*n*	Age (yr)	Height (cm)	Weight (kg)
Part 1				
Plain bupivacaine	11	29 ± 1	164 ± 2	76 ± 3
Bupivacaine + epinephrine	17	29 ± 1	165 ± 2	77 ± 3
Part 2				
2-CP test	15	28 ± 1	164 ± 2	74 ± 3
Lidocaine test	15	28 ± 1	161 ± 1	81 ± 5

2-CP, 2-chloroprocaine.
There were no significant differences.

Table 3. Bupivacaine Dose

Group	Initial dose (mg)	Redose (mg)	Redose required (%)	Total dose (mg)
Part 1				
Plain bupivacaine	141 ± 8	47 ± 6	64	169 ± 11
Bupivacaine + epinephrine	115 ± 4^a	42 ± 5	35	129 ± 5^a
Part 2				
2-CP test	142 ± 6	45 ± 6	47	163 ± 9
Lidocaine test	143 ± 4	45 ± 20	13^b	149 ± 4

2-CP, 2-chloroprocaine.
Doses are given as mean ± SEM.
^{a}$P < 0.05$ vs plain bupivacaine group.
^{b}$P < 0.05$ vs 2-CP test group.

panel). Addition of epinephrine also increased the time to two-segment regression of sensory blockade (49 ± 16 min in the plain bupivacaine group vs 80 ± 10 min in the epinephrine group; $P < 0.05$). The groups did not differ in duration of analgesia (Figure 1; median duration was 16 h in the plain bupivacaine group vs 18 h in the epinephrine group, P = NS), nor did they differ in intensity of analgesia as measured by pain scores (Table 4, upper panel). The groups did not differ in incidence of side effects (Table 5, upper panel), and no patient had a respiratory rate of <12 breaths/min.

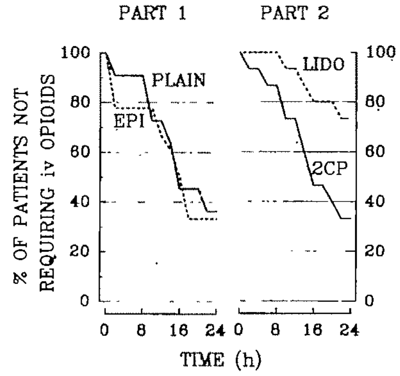

Figure 1. Duration of analgesia after epidural morphine injection in patients receiving intraoperative anesthesia with bupivacaine alone or with epinephrine (EPI) (*left panel*) and in patients receiving epidural catheter tip testing with 2-chloroprocaine (2CP) or lidocaine (LIDO) (*right panel*). Lidocaine group differs from 2-chloroprocaine group by log rank test ($P < 0.05$).

Part 2: Effect of 2-Chloroprocaine

Choice of local anesthetic for catheter testing did not affect the bupivacaine dose needed to establish sensory blockade to T-4 or total bupivacaine dose, although it did affect the number of patients receiving additional doses of bupivacaine (Table 3, lower panel). Time to two-segment regression of sensory blockade was similar in both groups (39 ± 8 min in the 2-chloroprocaine test group vs 59 ± 9 min in the lidocaine test group; P = NS). Epidural morphine analgesia did not differ in intensity, as measured by pain scores (Table 4, lower panel), but was of longer duration in the lidocaine test group compared with the 2-chloroprocaine test group (Figure 1; median duration was 16 h in the 2-chloroprocaine test group vs 24 h in the lidocaine test group, $P < 0.05$). The groups did not differ in incidence of side effects (Table 5, lower panel), and no patient had a respiratory rate of <12 breaths/min.

Discussion

Although morphine is frequently administered epidurally after cesarean section, there have been few examinations of factors affecting efficacy and side effects despite reported analgesia of highly variable duration and high incidence of side effects associated with such therapy. This study examines two factors affecting epidural morphine therapy and provides a rationale to enhance efficacy of this therapy.

Effects of Epinephrine

Epinephrine enhances analgesia of epidurally administered local anesthetics and opioids by delaying vascular absorption and/or by activating spinal α_2-adrenoceptors. Concurrent epidural or intrathecal administration of all three agents (opioid, local anesthetic, and epinephrine) enhances analgesia compared with any two (5), presumably by concurrent activation of separate analgesic systems. The effects of sequential injection of these agents have been the subject of few systematic investigations.

In this study, epinephrine, administered concurrently with bupivacaine, intensified anesthesia from bupivacaine but not analgesia from subsequently

Table 4. Percentage of Patients With Pain

Group	Comfortable (%)	Mildly uncomfortable (%)	Very uncomfortable (%)	In pain (%)
Part 1				
Plain bupivacaine	84	13	3	1
Bupivacaine + epinephrine	94	5	1	0
Part 2				
2-CP test	81	15	3	1
Lidocaine test	93	7	0	0

2-CP, 2-chloroprocaine.
Data expressed as percentage of observations.
There were no significant differences.

Table 5. Side Effects

Group	Sedation: Wide awake (%)	Sedation: Drowsy (%)	Sedation: Dozing (%)	Sedation: Asleep (%)	Nausea (%)	Pruritus (%)
Part 1						
Plain bupivacaine	68	8	16	7	72	100
Bupivacaine + epinephrine	68	15	9	7	53	76
Part 2						
2-CP test	69	11	14	7	53	60
Lidocaine test	63	22	8	7	87	60

2-CP, 2-chloroprocaine.
Sedation data expressed as percentage of observations. Nausea and pruritus data expressed as percentage of patients with these side effects.
There were no significant differences.

administered morphine. These results agree with previous work demonstrating enhancement of bupivacaine anesthesia by epinephrine (7). Although a previous study suggested enhancement of epidural morphine analgesia by previously administered epinephrine (2), a direct comparison was not performed in the latter study. Whereas spinal α-adrenergic and opioid systems have been demonstrated to be synergistic in producing analgesia in animals (8), this effect may not have been observed in the current study because of different time-courses of epinephrine and morphine actions or inadequate dose.

In volunteers, epidurally administered epinephrine alone produces segmental hypalgesia lasting 6 h without side effects and, in combination with morphine, enhances pruritus, nausea, and respiratory depression produced by morphine (9). The effects of sequential administration of epinephrine and morphine are less clear. Douglas et al. (3) examined the effect of the addition of epinephrine to bupivacaine on epidural morphine analgesia after cesarean section and observed an inverse correlation between epinephrine dose and intensity of pruritus. Their observation of less pruritus after 45 μg than after 15 μg of epinephrine is consistent with our observation of no increase in pruritus from epidurally administered morphine after prior injection of an even larger epinephrine dose (129 ± 5 μg).

Effects of 2-Chloroprocaine

2-Chloroprocaine interferes with analgesia provided by epidurally administered opioids. For example, duration of analgesia after epidurally administered morphine is decreased when 2-chloroprocaine is used to provide epidural anesthesia for cesarean section (10). Whereas one could argue that this is due to a window period of pain after rapid dissipation of 2-chloroprocaine anesthesia and prior to the onset of morphine's action, this is unlikely for two reasons. First, studies of epidural analgesia during labor suggest an active antagonism by 2-chloroprocaine (5). Second, in this study, the steady dropout of patients requesting supplemental analgesia suggested that the effect of epidural morphine was diminished throughout the 24-h period, not just during the first hours.

The etiology of 2-chloroprocaine-induced interference with the action of morphine is unclear. Apparently small doses are capable of producing this effect, as prior injection of only 140 mg interferes with the action of epidurally administered fentanyl during labor (5) and of morphine after cesarean section. The pH of the 2-chloroprocaine solution is not important in this antagonism (11). The long-acting inhibition may be due to a metabolite, and one such metabolite, 2-chloroaminobenzoic acid, is an opioid antagonist in dogs (12). (The printed abstract, submitted before completion of these studies, did not show antagonism. However, data presented at the Annual Meeting of the American Society of Anesthesiologists, when studies were completed, showed antagonism.) Alternatively, extracellular Ca^{2+} is required for the analgesic action of opioids in the spinal cord (13), and calcium chelation from disodium ethylenediaminetetraacetic acid in the 2-chloroprocaine solution may inhibit morphine's action.

Dose dependency and duration of 2-chloroprocaine's inhibition of epidural opioid analgesia have not been previously examined. Even small doses of 2-chloroprocaine (140 mg) diluted by subsequent bupivacaine injection diminish analgesia from epidurally administered fentanyl during labor (5), and this study suggests that similar doses, administered as much as 45–60 min before morphine, diminish epidural morphine analgesia throughout a 24-h period. This long-acting inhibition from even small doses suggests the action of a substance other than 2-chloroprocaine itself in accordance with functional studies (12).

It is of interest that 2-chloroprocaine diminished the analgesia produced by epidural morphine but not the side effects. This argues for a local, spinal opioid inhibition, as epidural opioid analgesia is primarily spinally mediated but nausea is due primarily to supraspinal actions (14). Similarly, time-courses of analgesia and nausea are in accordance with these sites of action, with early onset of analgesia and delayed onset of nausea. In contrast, pruritus occurred early and was prolonged, agreeing with production by both spinal and supraspinal mechanisms (15).

In summary, the analgesia and side effects produced by epidural morphine are unaffected by the addition of epinephrine to bupivacaine for intraoperative anesthesia. Even small doses of 2-chloroprocaine, such as those used to test epidural catheter tip location, interfere with epidural morphine analgesia and should be avoided if epidural morphine therapy is to be used.

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REGIONAL ANESTHESIA AND PAIN MANAGEMENT
Section Editor
Phillip O. Bridenbaugh

Differential Effects of Intrathecal Midazolam on Morphine-Induced Antinociception in the Rat: Role of Spinal Opioid Receptors

Anil K. Rattan, PhD, John S. McDonald, MD, and Gopi A. Tejwani, PhD
Departments of Anesthesiology and Pharmacology, The Ohio State University, College of Medicine, Columbus, Ohio

The antinociceptive effects of an intrathecally administered benzodiazepine agonist midazolam, alone and in combination with morphine, were examined in the rat by using the tail-flick test. The duration of antinociceptive effect produced by midazolam was significantly less ($P < 0.05$) than that produced by morphine. Low doses of midazolam (10 μg) and morphine (10 μg) produced a synergistic effect in prolonging antinociceptive effect. However, at higher doses (20 or 30 μg), these drugs reduced the extent of antinociception produced by each other. Naloxone administration prevented antinociception produced by these drugs, indicating interactions between midazolam and opioid receptors. Midazolam had dual effects on the binding of opioid ligands to the spinal opioid receptors. At low dose, it potentiated the displacement of [^{3}H]naloxone by morphine. At higher doses, midazolam inhibited the binding of opioid ligands to their spinal receptors in the following order: $\kappa > \delta > \mu$. These results indicate that differential antinociceptive effects of midazolam on morphine-induced antinociception involve interaction of this benzodiazepine with spinal opioid receptors.

(Anesth Analg 1991;73:124–31)

Many investigators have reported that intrathecally administered benzodiazepines such as midazolam modulate spinal antinociception (1,2). Midazolam has been shown to either increase or decrease spinal antinociception (3). Benzodiazepines have also been shown to produce antinociceptive action by binding to a specific receptor that is linked to GABA$_A$ receptor complex in the spinal cord (4–6). Recently, several investigators including ourselves have reported that administration of benzodiazepines such as midazolam can potentiate morphine-induced antinociception in various animal models (7–9). However, unlike Yanez et al. (9), we observed that midazolam can either increase or decrease spinal antinociception depending on the relative concentrations of morphine and midazolam in the subarachnoid space (8). The aim of the present study was to examine in detail the effect of intrathecal injection of various doses of midazolam on morphine-induced antinociception in the rat and to define the type of interaction between midazolam and morphine. Specifically, we investigated (a) whether the opiate antagonist naloxone reversed the antinociceptive effects produced by midazolam and/or morphine and (b) whether midazolam affected morphine-induced antinociception by altering the binding of opioid ligands to their receptors in the rat spinal cord. A preliminary report on this work has been presented (10,11).

Methods

Animals

Male Sprague-Dawley rats (Zivic-Miller Laboratories, Allison Park, Pa.) weighing 325–375 g were used. Before the start of the experiment, they were housed in groups of four in a room maintained at 22 ± 1°C with a 12-h on-and-off lighting schedule (12). All experiments, which were approved by the Ohio State University Institutional Laboratory Care and Use Committee, were performed between 8 AM and 2 PM. Laboratory rat food and water were given ad libitum.

Surgical Protocol

To implant an intrathecal catheter as described by Yaksh and Rudy (13), rats were anesthetized with ketamine (Vetalar, 80 mg/kg, IM) and xylazine

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Accepted for publication March 26, 1991.
Address correspondence to Dr. Tejwani, The Ohio State University, Department of Pharmacology, College of Medicine, 5197 Graves Hall, 333 West 10th Avenue, Columbus, OH 43210-1239.

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0003-2999/91/$3.50

(Rompum, 8 mg/kg, IM). Briefly, the head and the back of the neck were shaved and cleaned with 1% Podiodine solution, and the head was fixed in a stereotaxic instrument (David-Kopf Instruments, Tujunga, Calif.). After aseptic procedures, the cisternal membrane was exposed and the dura was cut rostrocaudally in the midline approximately 2–3 mm from the posterior rim of the foramen magnum. A 10-cm-long polyethylene catheter (PE-10, 0.61-mm outside diameter; Clay Adams, Parsippany, N.J.) was sterilized by immersion in 70% ethanol and then washed and flushed with sterile saline solution (0.9% NaCl) before use. The catheter was inserted into the spinal subarachnoid space through a slit made in the cisternal membrane and was advanced caudally with a slight rotation to a position that corresponded to L2 to L6 vertebrae. The external catheter was affixed to the skull by two screws fixed to the cranial surface with cranioplastic cement, and the external tip was closed with a knot. After the last injection, the animals were anesthetized with ketamine and xylazine, and 20 μL of 3% ferric chloride and 1% potassium ferrocyanide in 10% formaline solution was injected into the catheter to aid in the evaluation of catheter placement as indicated by a Prussian blue color. The animals were dissected, and the location of the catheter tip was verified. Data from the animals with malpositioned catheters were excluded from the study.

Injection Protocol and Antinociception Test

Intrathecal injections of drugs were made in a volume of 6 μL over a period of 1 min, preceded and followed by 5 μL of saline solution (vehicle) to clear the catheter. Control animals received only the vehicle. A different group of six rats was used for each trial. Initially, different doses of morphine sulfate (Winthrop Pharmaceuticals, New York, N.Y.) and midazolam-HCl (Hoffman-La Roche, Nutley, N.J.) were administered intrathecally using a Hamilton Microliter syringe (Hamilton Co., Reno, Nev.). The intrathecal volume injected was kept constant in all experiments. Naloxone-HCl (Sigma Chemicals, St. Louis, Mo.) was dissolved in 0.9% sterile saline solution and used as indicated in the figure legends to determine the involvement of opiate system in mediating spinal antinociception. The rats were tested for their nociceptive responses using the thermally evoked tail-flick test before and at indicated times after drug administration. The tail-flick test was conducted with a Tail-flick Analgesia Meter (IITC, Woodland Hills, Calif.). The rheostat-controlled light (sensitivity 5, beam at 90%) was focused at the tail (5–7 cm from the tip), and the time interval from the onset of the heat stimulus to the flick of the tail was recorded automatically by the instrument. A cut-off time of 10 s was used to avoid tissue damage caused by intense heat (14).

Spinal Opioid Receptor Assay

Normal rats not injected with any drugs were killed by decapitation, and the spinal cords were isolated and immediately frozen in liquid nitrogen until they were analyzed for activity of opioid receptors. Briefly, the spinal cords were homogenized in 50 mM Tris-HCl buffer, pH 7.5 (100 mg wet wt/mL), and the homogenate was centrifuged at 49,000 *g* for 15 min at 4°C. The supernatant was decanted and the pellet was homogenized in its original volume of 50 mM Tris-HCl buffer. This step was repeated, and the homogenized pellet was incubated at 37°C for 40 min to remove and degrade the endogenous opioid peptides from the receptor sites. The final suspension was centrifuged at 49,000 *g* for 15 min at 4°C, and the pellet was homogenized in 22 mL of 50 mM Tris-HCl buffer per 250 mg original tissue wet weight (15,16). Assays using spinal cord membrane suspensions (1 mL, consisting of about 1 mg protein) were performed in duplicate. The opioid ligands [^{3}H]naloxone (specific activity, 40.5 Ci/mmol), [^{3}H]morphine (specific activity, 86.2 Ci/mmol), [^{3}H]Tyr-D-Ala-Gly-Methyl-Phe-Glyol-enkephalin (DAGO; specific activity, 32.1 Ci/mmol), [^{3}H]Tyr-D-Ser-Gly-Phe-Leu-Thr-enkephalin (DSTLE; specific activity, 32.1 Ci/mmol), and [^{3}H]ethylketocyclazocine (EKC; specific activity, 25.3 Ci/mmol) were obtained from New England Nuclear, Boston, Mass. These ligands were incubated for 1 h at 25°C with spinal membrane suspensions in the presence and absence of nonradioactive ligands as indicated in the figure legends and were diluted in 50 mM Tris-HCl buffer. Morphine and midazolam solutions were made fresh every day. The suspensions were then rapidly filtered on Whatman GF/B filters, using a Brandel cell harvester to trap the labeled membranes, followed by three 3-mL washes with ice-cold 50 mM Tris-HCl buffer, pH 7.5. The filters were placed in vials containing 3 mL of liquid scintillation mixture and were counted in a Beckman liquid scintillation counter. Specific binding was defined as the difference between the amount bound in the absence and presence of 1 μM levorphanol for naloxone and morphine, of 500 nM DAGO for μ-receptors, of 500 nM DSTLE for δ-receptors, and of 500 nM ethylketocyclazocine for κ-receptors (16). (Specific binding = total binding − nonspecific binding.) When [^{3}H]EKC was used, 100 nM each of DAGO and DADLE (Tyr-D-Ala-Gly-Phe-D-Leu-enkephalin) were included in the assay mixture to suppress the binding of this ligand to μ- and δ-receptors.

Statistical Analysis

Tail-flick response latencies are presented as mean ± SEM. Comparisons between predrug and postdrug treatment were carried out with a one-way analysis of variance (ANOVA) followed by the Newman-Keuls t-test. In analysis of the relationship between the effects of drugs on tail-flick, latencies were converted to percentage maximal possible effect (MPE), where

$$\%\ \text{MPE} = \frac{\text{Postdrug latency} - \text{Predrug latency}}{\text{Cut-off time} - \text{Predrug latency}} \times 100.$$

P-values less than 0.05 were considered to be statistically significant.

The IC_{50} values of the morphine and midazolam were determined on an IBM PC computer using a GraphPAD InPlot program and nonlinear regression (15,16).

Results

Antinociception Produced by Midazolam and Morphine

Intrathecally administered midazolam produced a dose-dependent increase in the tail-flick latency, the peak antinociceptive effect being observed 20 min after the administration of the drug (Figure 1A). In contrast, morphine-induced antinociception was apparent even 6 h after the administration of the drug (Figure 1B). To investigate the effect of midazolam on morphine-induced antinociception, we used three different doses of midazolam (10, 20, and 30 μg) at three increasing concentrations of morphine as shown in Figure 2. Ten micrograms of midazolam (Figure 1A) or morphine (Figure 2A), which by themselves did not produce a significant antinociceptive effect, when given together synergistically increased antinociception which lasted up to 1 h (Figure 2A). However, 20 or 30 μg of midazolam, when administered with 20 μg (Figure 2B) or 30 μg of morphine (Figure 2C), significantly ($P < 0.05$) decreased morphine-induced antinociception. This inhibition was more apparent between 2 and 6 h after injection of these drugs (Figure 2B,C). This antagonistic effect of midazolam on morphine antinociception was not reported by Yanez et al. (9) as they did not use sufficiently higher doses of midazolam or morphine.

Naloxone Abolishes Midazolam- and/or Morphine-Induced Antinociception

To investigate whether midazolam affected morphine-induced antinociception by interaction with the spinal opioid receptors, we used naloxone, a pure opioid receptor antagonist. As shown in Figure 3, intrathecal injection of 100 μg of naloxone, which by itself had no effect on basal antinociception, abolished morphine- as well as midazolam-induced antinociception ($P < 0.05$). Antinociception produced by giving midazolam and morphine together was also decreased by 69% ($P < 0.05$) in the presence of naloxone (Figure 3), indicating possible interaction of midazolam with opioid receptors. In contrast to results obtained with intrathecal injection of naloxone in abolishing midazolam-induced antinociception (Figure 3), intraperitoneal injection of naloxone (1 mg/kg) has been shown not to affect the antinociception produced by a high (100 μg) dose of midazolam alone (9).

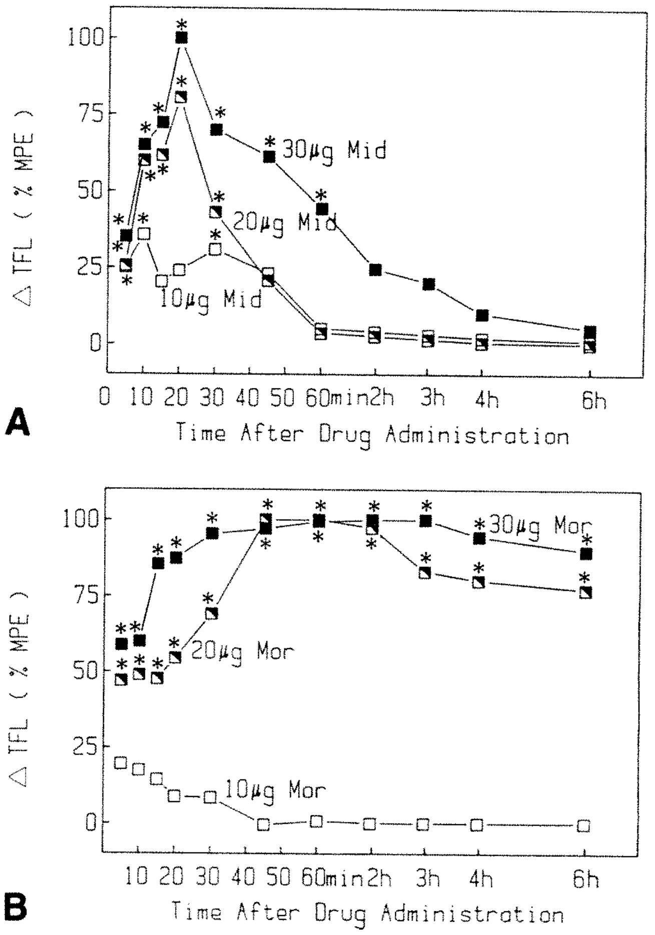

Figure 1. Dose- and time-dependent antinociception produced by midazolam (**A**) and morphine (**B**). Midazolam or morphine was administered intrathecally. Each point represents percentage maximum possible effect (% MPE), as mean of tail-flick latency (TFL) obtained from six or more rats. Significant differences were obtained by the Newman-Keuls t-test following a significant ANOVA. $^*P < 0.05$ (compared with animals injected with saline solution at their respective times).

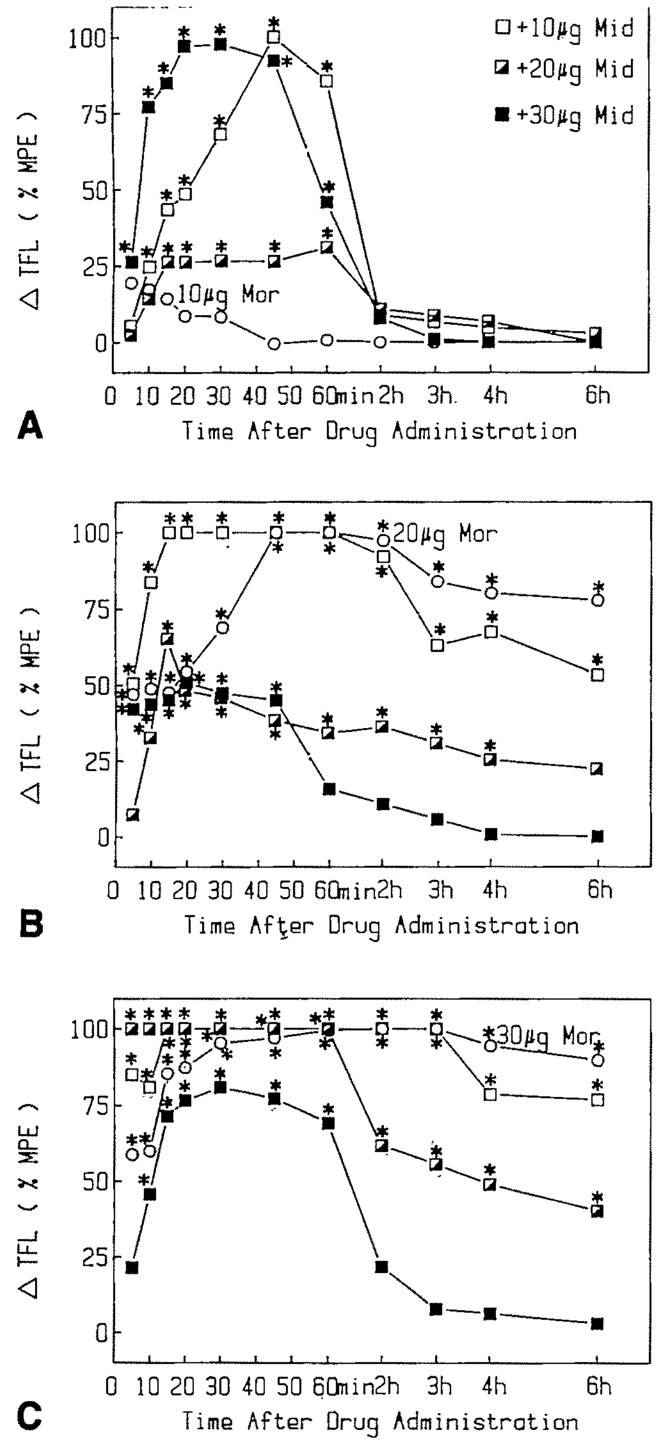

Figure 2. Comparative effect of morphine alone (*open circles*) and in combination with midazolam (*squares*) in producing antinociception after intrathecal injections. **A.** Morphine alone (○, 10 μg) and in the presence of different doses of midazolam (□, 10 μg; ◩, 20 μg; ■, 30 μg). **B.** Morphine alone (○, 20 μg) and in presence of different doses of midazolam (□, 10 μg; ◩, 20 μg; ■, 30 μg). **C.** Morphine alone (○, 30 μg) and in presence of different doses of midazolam (□, 10 μg; ◩, 20 μg; ■, 30 μg). Significant differences were obtained by the Newman-Keuls *t*-test following a significant ANOVA. $^*P < 0.05$ (compared with animals injected with saline solution at their respective time). (TFL, tail-flick latency.)

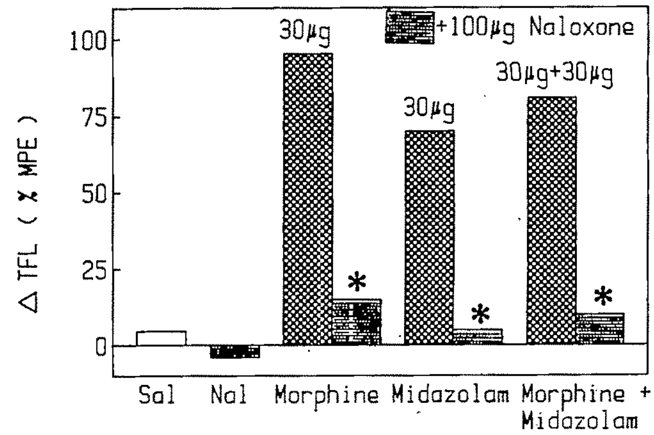

Figure 3. Effect of naloxone on morphine- and/or midazolam-induced antinociception. Saline solution (Sal, 0.9% NaCl) and naloxone (Nal, 100 μg) were given intrathecally. Naloxone inhibited antinociception produced by morphine (30 μg), midazolam (30 μg), or both together (30 μg each). *Criss-cross bar* shows the effect of drug only and *speckled bar* shows the effect with naloxone administration 15 min before the drugs were injected; the recordings were made 15 min after administration of midazolam, morphine, or both together. Significant differences were obtained by the Newman-Keuls *t*-test following a significant ANOVA. $^*P < 0.05$ (compared with morphine, midazolam, or morphine + midazolam, respectively). (TFL, tail-flick latency.)

Effect of Midazolam on the Binding of Opioid Ligands to Their Receptors

To determine whether midazolam potentiated morphine antinociception (Figure 2A) by enhancing the binding of morphine to opioid receptors, we determined the effect of morphine alone, midazolam alone, and both morphine and midazolam together on the binding of [^{3}H]naloxone to spinal opioid receptors (Figure 4). Low concentrations of midazolam (50 or 100 nM) did not affect the binding of [^{3}H]naloxone to opioid receptors. Morphine (50 or 100 nM) inhibited the specific binding of [^{3}H]naloxone to opioid receptors in the spinal cord by 51% and 62%, respectively ($P < 0.05$) (Figure 4). But when both the drugs were used together, they decreased the binding of [^{3}H]naloxone significantly ($P < 0.05$) more than the decrease in binding observed with morphine alone. There were significant differences ($P < 0.05$) in values of specific binding of [^{3}H]naloxone in the presence of morphine and midazolam when compared with morphine alone especially at the 50 and 100 nM concentration of drugs (Figure 4). These results suggest that midazolam at low concentrations (50 or 100 nM) facilitates the displacement of opiate antagonist (naloxone) by an opiate agonist (morphine) from the spinal opioid receptors by facilitating the binding of morphine.

To assess whether the inhibition of morphine-induced antinociception with 20 or 30 μg of midazo-

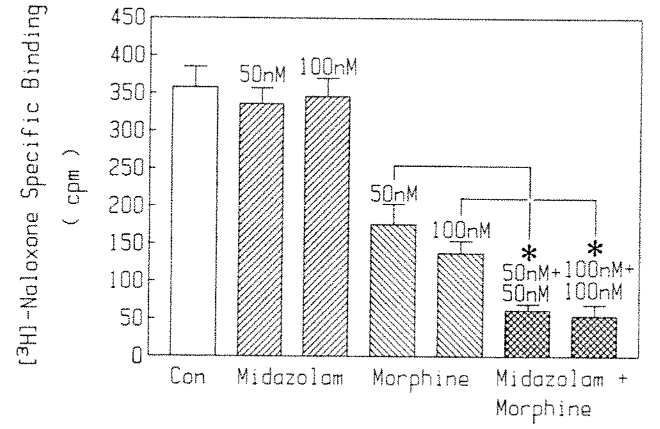

Figure 4. Effect of midazolam alone, morphine alone, and midazolam and morphine together on the binding of [^{3}H]naloxone to opioid receptors in spinal cord membranes of the rat. Midazolam potentiated the displacement of [^{3}H]naloxone by morphine. The values are [^{3}H]naloxone specific binding (counts per minute) of at least three or more experiments performed in duplicates. The experiments were performed as described in Methods. Significant differences were obtained by the Newman-Keuls *t*-test following significant ANOVA. $^*P < 0.05$ (Con, control.)

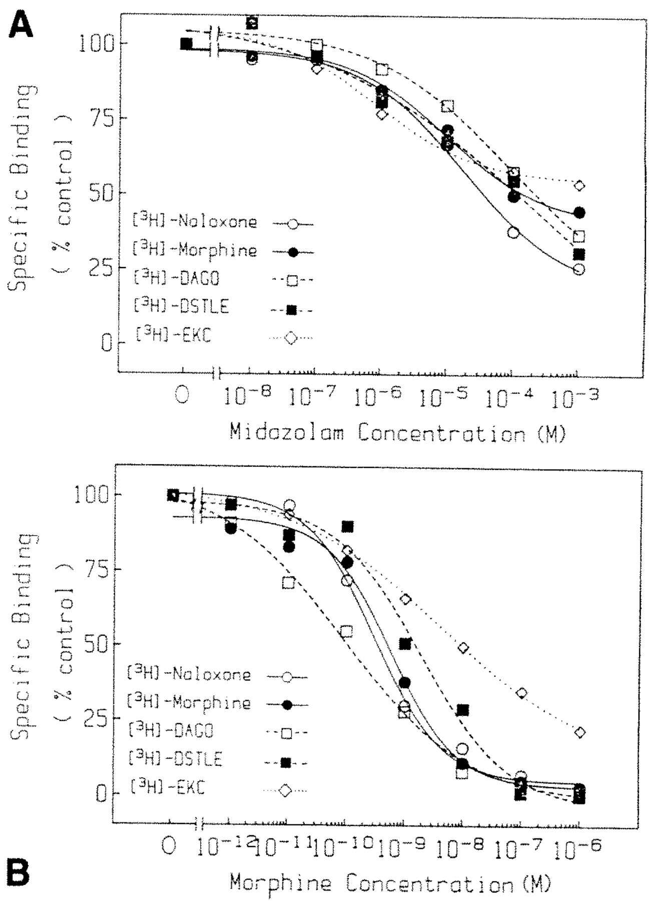

Figure 5. Effect of midazolam (**A**) and morphine (**B**) on the binding of ligands to various subtypes of spinal opioid receptors. The concentration of ligands used was [^{3}H]naloxone (0.5 nM), [^{3}H]morphine (0.5 nM), [^{3}H]DAGO (1 nM), [^{3}H]DSTLE (1 nM), and [^{3}H]EKC (2 nM). The values shown are the mean of three or more experiments as the percentage control of specific binding. Inter-experimental variations in the values were less than 10%. The dose-response curves were determined on the IBM PC computer using the GraphPAD program and nonlinear regression. The IC_{50} values for different ligands are given in Table 1.

lam (Figure 2B,C) was due to the inhibition of spinal opioid receptors by midazolam, we determined the midazolam effect on the binding of specific ligands to various opioid receptors. With the intrathecal injection of 20 or 30 μg of midazolam into the subarachnoid space where cerebrospinal fluid volume is about 50–100 μL, the midazolam concentration achieved is in the range of 1 μM. As shown in Figure 5A, midazolam doses given in this range inhibited the specific binding of [^{3}H]naloxone, [^{3}H]morphine, [^{3}H]DAGO (μ-receptors), [^{3}H]DSTLE (δ-receptors), and [^{3}H]EKC (κ-receptors). In contrast, morphine inhibited the specific binding of these ligands at much smaller concentrations (Figure 5B). A comparison of the IC_{50} values of morphine and midazolam shown in Table 1 indicates that morphine has 49, 591, and 22,993 times greater affinity than midazolam for κ-, δ-, and μ-spinal opioid receptors, respectively, and that midazolam affinity for κ-receptors > for δ-receptors > for μ-receptors.

Discussion

Epidural or intrathecal postoperative injection of opiates produces analgesia associated with improved pulmonary function and with a decreased incidence of pulmonary complications when compared with systemically administered opiates (17–21). The analgesic effect of morphine, the epidural opiate most frequently used, is due to its low lipid solubility, its extensive distribution in cerebrospinal fluid, and its binding to spinal opioid receptors (18). Midazolam is a potent benzodiazepine with hypnotic, sedative, anxiolytic, and muscle relaxant properties, which, in addition to its rapid onset and relatively short duration of action, make it a suitable agent for induction of general anesthesia (22,23). Combinations of benzodiazepines and opiates are commonly used intravenously. Tverskoy et al. (24) have recently reported that interactions between midazolam and morphine, when used to produce sedation, represent a summation of their effects.

Results of studies on interactions between benzodiazepines and morphine in producing analgesia are controversial. For example, diazepam has been found to decrease (25–27), increase (7,28,29), or have no effect (30) on morphine-induced antinociception. We were interested in the reasons for these discrepancies. Daghero et al. (31) reported that midazolam

Table 1. The Inhibition of the Binding of [^{3}H]Naloxone, [^{3}H]Morphine, [^{3}H]DAGO, [^{3}H]DSTLE, and [^{3}H]EKC to Spinal Cord Opioid Receptors of Rat by Morphine and Midazolam at IC$_{50}$ (nM)

	IC$_{50}$ (nM)		
Ligands	Morphine	Midazolam	Fold difference
[^{3}H]Naloxone (0.5 nM)	2.89 ± 0.31	13,510 ± 4,050	4,675
[^{3}H]Morphine (0.5 nM)	6.14 ± 0.79	9,480 ± 290	1,544
[^{3}H]DAGO (1 nM)	1.47 ± 0.32	33,800 ± 1,350	22,993
[^{3}H]DSTLE (1 nM)	13.71 ± 2.74	8,100 ± 560	591
[^{3}H]EKC (2 nM)	14.35 ± 4.02	700 ± 280	49

IC$_{50}$, concentration of morphine and midazolam that caused 50% inhibition of the ligands' binding; DAGO, Tyr-D-Ala-Gly-Methyl-Phe-Glyol-enkephalin; DSTLE, Tyr-D-Ser-Gly-Phe-Leu-Thr-enkephalin; EKC, ethylketocyclazocine.

The IC$_{50}$ values are the mean ± SD of at least two experiments performed in duplicate and were determined on the IBM PC computer using the GraphPAD program and nonlinear regression.

(0.5 mg/kg, IP) antagonized the antinociceptive effect of morphine (1 mg/kg, SC). Bergman et al. (7) reported that pretreatment with diazepam (1 mg/kg, IP) significantly enhanced the antinociceptive effects of morphine (2–11 mg/kg, IV). We believe that the effect of midazolam on morphine antinociception when injected intrathecally depends on the dose of midazolam and particularly on the concentration of midazolam in comparison with that of morphine. For example, we observed that 10 μg each of morphine and midazolam have a synergistic effect in increasing antinociception (Figure 2A); however, when these drugs are used at the dose of 20 μg or more, midazolam inhibits antinociception produced by morphine (Figure 2B,C). These results suggest that midazolam at high concentration is capable of blocking opiate-induced antinociception.

Recently, Rosland and Hole (32) reported that intraperitoneal injections of diazepam and midazolam antagonized antinociception produced in the rat by subcutaneous injections of morphine, fentanyl, or buprenorphine. They proposed that this antagonism represents an interaction between benzodiazepines and the opioid system in the brain participating in modulation of nociceptive inputs but have given no direct experimental support for the existence of such interactions between benzodiazepine and opioid receptors. Similarly, Kissin et al. (33) have provided no mechanism for the occurrence of relative antagonism between morphine and fentanyl, on one hand, and diazepam, on the other hand, regarding movement in response to noxious stimulation. One obvious issue is the ability of midazolam to interact with opioid receptors. We observed that midazolam-induced antinociception was antagonized by naloxone, suggesting an involvement of opioid receptors in midazolam-induced antinociception (Figure 3). At low concentration, midazolam enhances morphine-induced antinociception. This observation is consistent with clinical data showing that the combined use of midazolam with opiates results in an increase in the opiate-induced analgesia (34,35). An overlap in the distribution of opioid and benzodiazepine receptors in the spinal cord has been reported. The dorsal horn of the spinal cord, especially the substantia gelatinosa, has been shown to possess both opioid and benzodiazepine receptors in large numbers (36,37). Therefore, it is possible that benzodiazepine receptor agonists such as midazolam act by modulating the antinociceptive effect of the opiates. In addition, depending on the dose of midazolam, this modulation will either enhance or depress opiate antinociceptive effects. We observed that morphine was more effective in displacing [^{3}H]naloxone from the spinal opioid receptors in the presence of midazolam than its absence. For example, the specific binding of [^{3}H]naloxone to spinal opioid receptors was lower in the presence of morphine and midazolam together than in the presence of either alone (Figure 4). These results suggest that in the presence of low concentrations of midazolam, opioid receptors are modulated in such a fashion that they have a higher affinity for morphine. It is possible that midazolam has a dual effect on the spinal opioid receptors. Low concentrations of midazolam favor the conformation of opioid receptors that have higher affinity for morphine, whereas high concentrations of midazolam inhibit opioid receptors. It is interesting to note that we have demonstrated for the first time, to the best of our knowledge, that midazolam at the concentrations we have used in subarachnoid space after intrathecal injections can inhibit the binding of specific ligands to μ-, δ-, and κ-spinal opioid receptors (Figure 5A and Table 1). This may explain the antagonism observed between midazolam and morphine in producing antinociception (Figure 2B,C). However, the affinity of midazolam for opioid receptors is considerably lower than that of morphine. The affinity of midazolam for μ-, δ-, and κ-receptors is 22,993, 591, and 49 times less respectively than the affinity of morphine for these receptors (Table 1). We believe that midazolam has more affinity for κ-receptors than it has for δ-receptors, and it has the least affinity for μ spinal receptors (Table 1). Our data also support the observation of Romer et al. (38) that opioid benzodiazepines such as tifluadom bind to κ-receptors.

In addition to the involvement of spinal opioid receptors in the facilitation of morphine-induced antinociception by midazolam (Figures 2A and 4) or its antagonism (Figures 2B,C and 5), it is plausible that other mechanisms reinforcing interactions between morphine and midazolam may exist. For example, it has been reported that acute intraperitoneal injection of morphine increases GABA content and activity of glutamate decarboxylase in the dorsal horn of the rat spinal cord (39). As potentiation of GABAergic inhibitory neurons in the spinal cord has been shown to increase the extent of antinociception and as midazolam has been shown to produce its antinociceptive effect by increasing the efficacy of GABA (40), it is conceivable that morphine-induced increase in the content of GABA in the spinal cord (39) may promote the synergistic antinociceptive effect produced by morphine and midazolam. On the other hand, a separate mechanism may operate to promote the antagonistic effect of midazolam on morphine antinociception. Morphine has been shown to bind to two different receptor sites. At low concentration it binds only to central nervous system opioid receptors but at high concentrations it blocks $GABA_A$ receptors (41,42) involved in GABA- and benzodiazepine-mediated antinociception. Thus, it is possible that opposite effects produced by midazolam and morphine on GABA receptor ionophore complex (increase in the efficacy of GABA by midazolam and blocking of $GABA_A$ receptor by morphine) are responsible for the observed antagonistic effects on antinociception (Figure 2B,C).

In conclusion, we found that intrathecal injections of midazolam can either increase or decrease morphine-induced antinociception in the rat. The extent of interactions between these two drugs depends on their concentrations in the subarachnoid space. We also have demonstrated a direct effect of midazolam on the binding of opioid ligands to their spinal opioid receptors, which may explain the molecular basis of interactions between midazolam and morphine in producing antinociceptive effects.

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Comparison of Continuous Epidural Bupivacaine Infusion Plus Either Continuous Epidural Infusion or Patient-Controlled Epidural Injection of Fentanyl for Postoperative Analgesia

Daniel Boudreault, MD, FRCPC, Louis Brasseur, MD, Kamran Samii, MD, and Jean-Pierre Lemoing, PhD

Département d'Anesthésie-Réanimation, Université Paris-Sud, Hôpital de Bicêtre, Kremlin Bicêtre, France; Janssen Research Foundation, Aubervilliers, France

We compared the postoperative epidural analgesia provided by the continuous epidural infusion of bupivacaine supplemented with patient-controlled injection (PCA) of epidural fentanyl with that provided by a continuous infusion of bupivacaine supplemented with a continuous epidural infusion of fentanyl. Our patient population comprised 16 ASA physical status I or II patients undergoing laparotomy with a midline incision under general anesthesia combined with bupivacaine epidural analgesia. Postoperatively, a continuous epidural infusion of bupivacaine ($0.1\ \mathrm{mg \cdot kg^{-1} \cdot h^{-1}}$) was combined with epidural fentanyl given by either (a) PCA (15-μg bolus with a lockout interval of 12 min, $n = 8$) or (b) continuous infusion ($1\ \mu\mathrm{g \cdot kg^{-1} \cdot h^{-1}}$, $n = 8$). In the case of inadequate pain relief in the latter group, the fentanyl infusion rate was increased by 10 μg/h. Analgesia evaluated by a visual analogue pain score and by a verbal pain score was similarly effective in both groups. The sedation score was also similar in both groups. The total dose of epidural fentanyl administered during the first 24 h was significantly lower in the PCA group than in the continuous infusion group (405 ± 110 μg vs 1600 ± 245 μg, $P < 0.001$). The dose of fentanyl given during each 4-h interval ranged between 40 and 160 μg in the PCA group and 251 and 292 μg in the continuous infusion group. Clinically detectable respiratory depression was not observed in either group. In conclusion, epidural administration of $0.1\ \mathrm{mg \cdot kg^{-1} \cdot h^{-1}}$ bupivacaine combined with fentanyl provides effective postoperative analgesia with a total dose of fentanyl required that is lower when fentanyl is administered by epidural PCA rather than by continuous epidural infusion.

(Anesth Analg 1991;73:132–7)

Epidural administration of opioids and patient-controlled analgesia (PCA) are two major advances in the management of postoperative pain. Patient-controlled analgesia has been used predominantly via the intravenous route (1–5), but more recently it has also been proposed for epidural administration of opioids (6). Using epidural hydromorphone by PCA, effective analgesia has been observed with smaller doses of opioids than with the usual continuous epidural infusion (7). However, hydromorphone is a long-acting opioid and may induce delayed respiratory depression (8,9). Shorter acting lipid-soluble opioids such as fentanyl may be a better alternative for epidural administration (10). Although the quality of afferent sensory neuronal blockade produced by epidural local anesthetics is good, that produced by the continuous administration of epidural fentanyl combined with epidural bupivacaine appears better for postoperative pain relief (11). In the present study of postoperative analgesia, we combined the continuous epidural administration of bupivacaine with two routes of fentanyl administration, PCA and continuous epidural infusion (12,13).

Methods

This study was approved by our local institutional ethical committee and informed consent was obtained from 16 ASA physical status I or II patients, 35–72 yr old, scheduled to undergo an elective laparotomy via a midline abdominal incision. Patients with any contraindications to epidural puncture, al-

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Accepted for publication April 4, 1991.

Address correspondence to Dr. Brasseur, Département d'Anesthesiologie, Hôpital de Bicêtre, Université Paris-Sud, 94275, Le Kremlin Bicêtre Cedex, France.

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0003-2999/91/$3.50

lergy to local anesthetics, a history of drug abuse, or known dependence on narcotics were excluded from the study.

All patients received 100 mg of oral hydroxyzine as a premedication 90–120 min before induction of anesthesia. An epidural catheter was inserted at the T-7 level, and the correct placement of this catheter was confirmed by the injection of 10–15 mL of 0.5% bupivacaine with 1:200,000 epinephrine before general anesthesia commenced. The injected dose of bupivacaine was determined so as to obtain a T4-5 level for upper abdominal surgery and a T8-9 level for lower abdominal surgery. General anesthesia was then induced with 1–3 μg/kg of fentanyl and 4 mg/kg of thiopental. Succinylcholine was used to facilitate tracheal intubation and anesthesia was maintained with N_2O/O_2 (60%/40%) and isoflurane (end-tidal values of 0.5%–0.8%) without fentanyl. During the operation 0.5% bupivacaine with 1:200,000 epinephrine was given as needed to maintain analgesia. Neuromuscular blockade was achieved with pancuronium or vecuronium and was antagonized at the end of the surgical procedure with neostigmine combined with an appropriate dose of anticholinergic agent.

The tracheas of all patients were extubated at the end of the operation, and the patients were transferred to the recovery room for the next 24 h. Pain control was achieved on arrival in the recovery room by the bolus injection of 8 mL of 0.25% epidural bupivacaine without epinephrine. Patients were then randomly allocated to study groups. Patients in the continuous infusion group ($n = 8$) were given a continuous epidural infusion of a mixture of 10 μg/mL of fentanyl in 0.1% bupivacaine at a rate of 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$. If this did not result in adequate postoperative pain relief, the rate of infusion was increased by 1 mL/h and a bolus of 8 mL of 0.25% bupivacaine was administered. Patients in the epidural PCA group ($n = 8$) were given a continuous epidural infusion of 0.1% bupivacaine at the same rate as in the continuous infusion group, i.e., [weight (kg)/10] mL/h combined with fentanyl administered by an epidural PCA infusion pump (BARD). The PCA device was set to deliver 15 μg (2 mL) of epidural fentanyl on demand, with a 12-min lockout interval and a 75-μg/h maximum dose. If the patient found that this regimen failed to provide adequate pain relief after 1 h, the bolus injection was increased by 0.5 mL (3.8 μg) each hour as needed to achieve adequate pain relief. Patients did not receive any other analgesics during the 24-h study period.

Postoperative vital signs (heart rate by ECG, arterial blood pressure by an automatic blood pressure device, respiratory rate by impedancemetry, and oxygen saturation with a Nellcor pulse oximeter) were recorded without stimulating the patients. Assessment of analgesia was made by using both a visual analogue scale (VAS 0–100) and a verbal pain scale (0, no pain; 1, mild; 2, moderate; 3, severe); assessment of sedation was made on a point scale (0, none; 1, mild; 2, moderate; 3, severe). Vital signs, pain scores, and sedation scores were recorded 1, 2, 4, 8, 12, 16, 20, and 24 h after the start of the postoperative analgesia and arterial blood samples were obtained at 0, 3, 6, 12, 18, and 24 h. Samples were immediately centrifuged and the plasma fraction was stored at −20°C for future radioimmunoassay determination of fentanyl levels (14). The minimum level of detection was 0.05 ng/mL; the coefficient of variation and accuracy were, respectively, 5%–10% and 98%–100%, in the range of calibration curves.

Data are expressed as mean ± SD. The significance of the differences between the two groups was analyzed using unpaired *t*-test for age, weight, height, sex, and duration of surgery. Pain and sedation scores at each time between the two groups were compared using the Mann-Whitney U-test; similarly, a Friedman test was used for comparing the evolution with time of VAS pain scores, verbal pain scores, and sedation scores; this test was applied to the two groups combined because the Mann-Whitney test failed to show any difference between the groups at any time when the different scores were considered. The Mann-Whitney U-test was used for comparing the total doses of fentanyl. $P < 0.05$ was considered statistically significant.

Results

Sixteen patients participated in the study: eight patients in the PCA group and eight in the continuous infusion group. There were no significant differences between the two groups with respect to age, sex, height, weight, and duration of surgery (Table 1).

Pain score evaluated by VAS and the verbal pain scale and sedation score were similar in both groups during the 24 h of the study (Figures 1–3). The mean maximum VAS in the epidural PCA group was, however, lower than in the continuous epidural infusion group (54 vs 78, $P < 0.05$).

Fentanyl doses given during each 4-h period (values ranging between 40 and 94 μg of fentanyl per 4 h in the PCA group and 251 and 292 μg of fentanyl per 4 h in the continuous infusion group) and the total doses of fentanyl given during the 24 h of the study were lower in the PCA group than in the continuous infusion group (405 ± 110 μg vs 1600 ± 245 μg, $P < 0.001$) (Figure 4). Despite the possibility of increasing the size of the PCA dose, no one needed the dose adjusted. However, six of eight patients in the continuous infusion group needed additional epidural analgesia to achieve adequate pain relief. The mean

Table 1. Demographic Data

	Epidural PCA (n = 8)	Continuous epidural infusion (n = 8)
Age (yr)	54.0 ± 11.9 (35–67)	58.8 ± 11.9 (43–72)
Sex		
Male	6	5
Female	2	3
Height (cm)	164.6 ± 8.6 (153–175)	164.8 ± 7.0 (152–175)
Weight (kg)	67.6 ± 16.7 (51–93)	62.9 ± 11.5 (45–82)
Duration of surgery (h)	4.7 ± 1.6 (2.5–7.0)	4.3 ± 1.6 (2.5–6.5)

PCA, patient-controlled analgesia.
Values are mean ± SD (range given in parentheses).
No significant difference between the two groups.

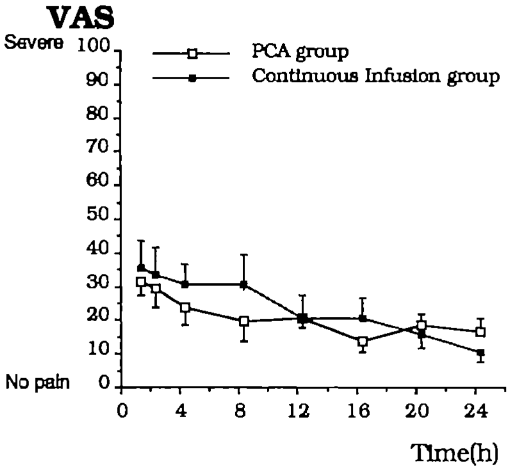

Figure 1. Pain score evaluated by VAS was similar in the continuous infusion and in the PCA groups (mean ± SEM).

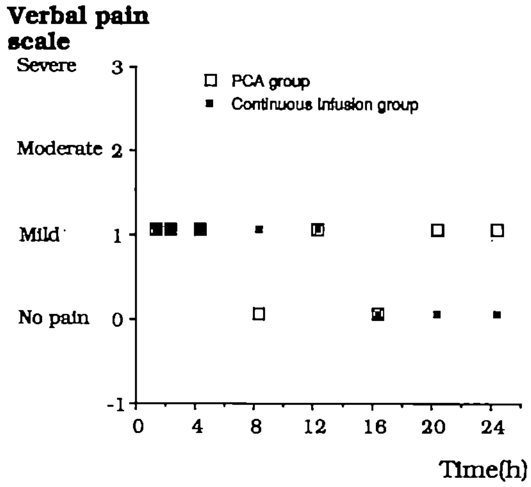

Figure 2. Pain score evaluated by verbal pain scale was similar in both groups (median values).

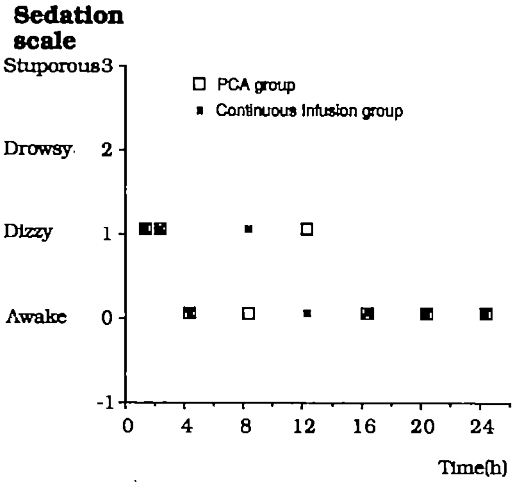

Figure 3. Sedation score was similar in both groups (median values).

fentanyl infusion rate was 1.13 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in the continuous infusion group and the maximal individual infusion rate was 1.45 $\mu g \cdot kg^{-1} \cdot h^{-1}$.

Mean plasma fentanyl levels in patients managed with epidural PCA were always significantly lower than those in patients in the continuous infusion group ($P < 0.05$, Figure 5).

The mean respiratory rates and oxygen saturation (Spo_2) levels were similar in both groups during the 24 h of the study. Respiratory rate was always ≥12 breaths/min and Spo_2 was always ≥92% (Table 2).

Discussion

Our study shows that postoperative analgesia is similar in patients receiving a continuous epidural infusion of bupivacaine supplemented by small doses of epidural fentanyl given by PCA and in those receiving epidural bupivacaine supplemented with much larger doses of epidural fentanyl given by continuous infusion.

We did not administer epidural fentanyl alone but combined it with the continuous administration of bupivacaine. The combination has been proposed to achieve a greater degree of analgesia while reducing the incidence of side effects (12,13). Previous studies also have demonstrated that fentanyl enhances and prolongs the analgesia achieved by bupivacaine alone. Experimental studies have shown that injury leads to a state of pain hypersensitivity by decreasing nociceptive thresholds peripherally and in the spinal cord (15) and that the spinal dorsal column receptive fields enlarge with time in the presence of nociceptive stimuli (16). It is possible that spinal nerve blockade

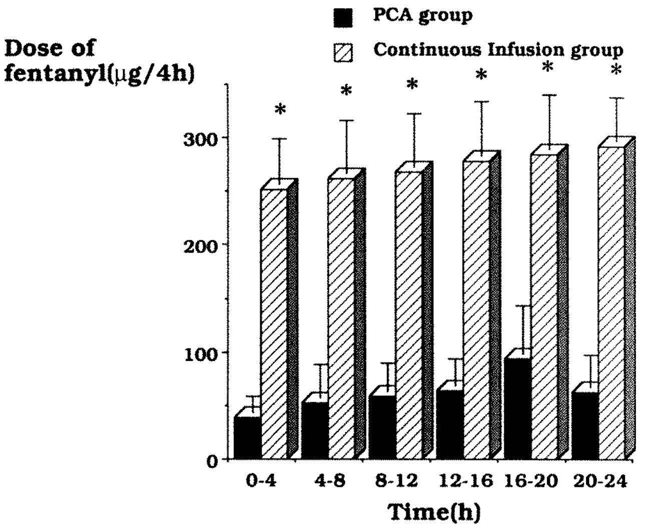

Figure 4. Mean doses (±SD) of fentanyl given at 4-h intervals in the PCA group were always lower than in the continuous infusion group. (*$P < 0.001$.)

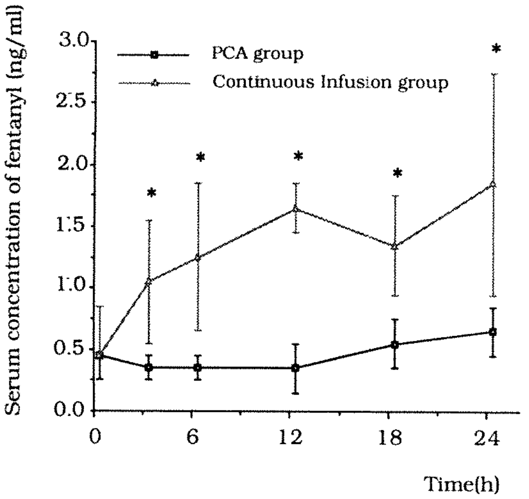

Figure 5. Comparison of serum concentration (ng/mL) obtained with PCA and continuous infusion of fentanyl epidurally for equal postoperative analgesia (mean ± SD). (*$P < 0.05$.)

diminishes in the presence of unaltered local anesthetic doses because of the resulting competitive increase in afferent input (17). Extradural morphine inhibits nociceptive transmission and the resulting decrease in afferent input may restore and maintain sensory levels of analgesia produced by epidural local anesthetics (18). This has not yet been demonstrated with fentanyl but we can assume that the same mechanism is involved. The dose of bupivacaine that we used, 0.1 mg·kg^{-1}·h^{-1}, was lower than the usual doses of bupivacaine recommended when it is used alone. Scott (17) has shown that 0.25 mg·kg^{-1}·h^{-1} of bupivacaine given epidurally is frequently insufficient to provide prolonged stable postoperative analgesia and that there is a considerable attenuation of effect with time. Thus, the small dose of bupivacaine we administered was alone probably not able to provide effective analgesia over a period of 24 h and a third group treated only with 0.1 mg·kg^{-1}·h^{-1} of epidural bupivacaine would have been ethically unacceptable. To improve analgesia in patients treated by fentanyl infusion and still in pain, a bolus of 8 mL of 0.25% bupivacaine was given and an increase of 1 mL/h of the infusion mixture was started. The reason for this approach was to obtain pain relief rapidly and to prevent the large increase in plasma fentanyl concentration that results from additional bolus injections of fentanyl.

The dose of fentanyl required to provide effective analgesia by epidural PCA was approximately one-third the dose used in the continuous epidural infusion group. Such a difference could be due to an overestimation of the need of the patients in the continuous infusion group. However, this is unlikely for two reasons: (a) the 1-µg·kg^{-1}·h^{-1} dose of fentanyl that we infused epidurally in the continuous infusion group was similar to doses that have been recommended previously, ranging between 1 and 1.5 µg·kg^{-1}·h^{-1} (19,23), and (b) even with a basal infusion rate of 1 µg·kg^{-1}·h^{-1}, six of eight patients in the continuous infusion group needed increases in the initial infusion rate because of persistent pain. Thus, overestimation of the need for fentanyl in the continuous infusion group could only have involved two patients. The mean dose administered in this group during the 24 h of our study was 1.13 µg·kg^{-1}·h^{-1} and even reached 1.45 µg·kg^{-1}·h^{-1} in one patient. Thus, the low total dose of fentanyl given in the PCA group was not due to an overdose of fentanyl in the continuous infusion group but to the relatively lower fentanyl requirements attendant on PCA use. Fentanyl requirements were low during the entire 24 h of the study as evidenced by the fact that the highest fentanyl dose needed by any patient in the PCA group was 165 µg/4 h. This was much lower than the maximum dose of 300 µg/4 h allowed by the PCA pump setting (15 µg/12 min).

Decreased opioid demand when PCA is used has already been reported either when opioids are administered intravenously or epidurally as a continuous infusion (7). There may be two reasons for this phenomenon: (a) a psychological mechanism related to the PCA device which allows self-control of the patient's pain and (b) a pharmacologic mechanism. The nonpharmacologic mechanism induced by PCA devices is probably a factor. Anxiety is a well-known characteristic of acute pain (24). Thus, permitting patients to participate actively in their pain control through use of epidural PCA could contribute to reduced opioid requirements (25). The reduction of

Table 2. Respiratory Rate and Oxygen Saturation in the Continuous Infusion and in the Patient-Controlled Analgesia Groups

	1 h	2 h	4 h	8 h	12 h	16 h	20 h	24 h
O_2 saturation (%)								
CI	97.5 ± 1.2	98.1 ± 1.6	97.8 ± 1.9	96.8 ± 2.0	97.1 ± 2.0	97.5 ± 1.8	96.3 ± 2.3	96.4 ± 1.3
PCA	97.5 ± 1.9	96.0 ± 1.5	96.3 ± 2.4	95.9 ± 1.7	95.8 ± 1.9	95.0 ± 2.5	95.8 ± 2.4	95.5 ± 2.0
Respiratory rate (min^{-1})								
CI	19.5 ± 5.6	22.0 ± 5.8	20.6 ± 5.3	21.5 ± 5.8	21.8 ± 6.3	21.9 ± 5.1	24.1 ± 5.1	21.6 ± 4.4
PCA	20.4 ± 4.3	19.6 ± 4.2	20.8 ± 3.8	20.6 ± 3.9	22.4 ± 2.9	19.6 ± 4.5	21.9 ± 4.1	21.8 ± 3.7

CI, continuous infusion; PCA, patient-controlled analgesia.
Values are mean ± SD.
No signifícnt difference between the two groups.

anxiety may enhance the placebo effect (26), and sophisticated scientific equipment may further contribute to increased therapeutic potential (27). Another possible explanation for the lower fentanyl requirements observed in the PCA group is pharmacologic. Plasma fentanyl levels observed in the PCA group were lower than in the continuous infusion group, eliminating a possible systemic mechanism. A mechanism at the level of the spinal cord is, however, possible. Bolus epidural injections of fentanyl may provide better cerebrospinal fluid penetration and spinal cord absorption than does continuous epidural infusion. With the latter technique, fentanyl may be partially absorbed by fat within the epidural space. Indeed fentanyl, which is highly lipophilic, could bind to lipid-containing structures of the spinal cord and epidural fat, thereby allowing less free fentanyl to migrate into the cerebrospinal fluid (12). It has been emphasized recently that fentanyl acts mainly through a systemic mechanism. This hypothesis could explain the finding in our study that analgesia was equal with epidural fentanyl when given by repeated small boluses despite much smaller total doses. However, comparative data on fentanyl cerebrospinal fluid concentration obtained by PCA and continuous infusion are not available to verify this hypothesis.

No severe side effects were observed in our study. However, we cannot conclude from this that both PCA and continuous infusions of fentanyl are safe. Indeed, the number of patients studied was limited and thus, a β or type II statistical error is possible. Also, we did not study control of ventilation. Using a dose of 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of epidural fentanyl, Renaud et al. (29) observed a significant decrease in the ventilatory response to CO_2 after several hours of infusion but without a decrease in respiratory rate. The absence of a decrease in respiratory rate in our study, although encouraging, does not permit us to eliminate respiratory depression leading to apnea as a potential complication. However, since (a) lower doses of fentanyl given by PCA are as efficient for analgesia as are higher doses given by continuous infusion and (b) the side effects of epidural opioids are dose-dependent, the use of PCA for epidural infusion of fentanyl seems to offer an advantage in reducing the risk of this complication.

In conclusion, epidural administration of small doses of bupivacaine combined with fentanyl provides effective postoperative analgesia with a smaller dose of fentanyl when administered by PCA than by continuous infusion.

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Can Galvanic Skin Response Be Used as a Quantitative Estimate of Sympathetic Nerve Activity in Regional Anesthesia?

Klaus Kirnö, MD, Masanari Kunimoto, MD, Stefan Lundin, MD, PhD,
Mikael Elam, MD, PhD, and B. Gunnar Wallin, MD

Departments of Anesthesia and Intensive Care and of Clinical Neurophysiology, Sahlgren's Hospital,
Göteborg, Sweden

To study the relationship between skin sympathetic nerve activity and changes in skin resistance (galvanic skin response—GSR), efferent sympathetic and sensory nerves to the hand were blocked by an axillary nerve blockade in 15 healthy subjects. Subsequently, intraneural electrical stimuli in the median nerve distal to the axillary nerve block were used to evoke changes in skin resistance and in water vapor partial pressure in the sensory and sympathetically denervated hand. With increasing frequency of stimulation, skin resistance decreased and water vapor partial pressure increased until stimuli exceeded 10 Hz. When an additional burst of impulses was added to the background stimulation, GSR amplitude varied in a nonlinear fashion with the background frequency. Stimulation-induced GSR was completely abolished in a dose-dependent manner by systemically (intravenously) administered atropine. The results indicate that GSR depends on the preceding level of nerve traffic in the sympathetic sudomotor nerve fibers. Consequently, skin resistance recordings cannot be used to quantify sympathetic nerve traffic and thus do not express the completeness of sympathetic blockade in regional anesthesia.

(Anesth Analg 1991;73:138–42)

Galvanic skin response (GSR) has been used as an indirect index of sympathetic activity (1–5). Based on studies showing a relatively good correlation between nerve activity in sympathetic sudomotor fibers and the amplitude of the corresponding changes in skin resistance (6,7), GSR has been used for quantifying sympathetic nerve activity in clinical studies of regional anesthesia and pain (8,9). Sometimes, however, the relationship between nerve traffic and GSR amplitude shows a pronounced scatter. During regression of epidural blockade, we noticed that GSRs evoked by arousal stimuli (i.e., sudden unexpected sounds or touches and forced arithmetics) had higher amplitudes than they had before blockade despite similar or lower mean voltage amplitudes of the sympathetic bursts (10). This finding suggests a nonlinear relationship between changes in skin resistance and sympathetic sudomotor nerve activity.

Unfortunately, multiunit sympathetic skin nerve recordings are not well suited for quantification of sudomotor neuroeffector function. Vasoconstrictor and sudomotor fibers, which are intermingled in cutaneous nerves, are often simultaneously activated and, as the impulses cannot be separated in the neurogram, a true estimate of sudomotor activity is difficult to obtain. Wallin and coworkers (11) approached the problem of quantifying sudomotor activity differently. Instead of trying to distinguish sudomotor impulses in naturally occurring discharges, they activated sudomotor fibers in the median nerve by intraneural electrical stimulation and measured the resulting change in skin resistance in the hand. A proximal nerve blockade of sympathetic and somatic sensory fibers was used to eliminate interference with spontaneous nerve activity and to block the pain produced by peripheral stimulation.

In the present study, a similar technique has been used to study the relationship between different levels of sympathetic nerve activity and corresponding changes in skin resistance. Atropine, a drug widely used in anesthetic practice, is known to affect

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Supported by grants from the Swedish Medical Research Council (No. B 91-04X-03546-20A and B 91-17X-08682-03A), from the Medical Faculty at the University of Göteborg, and from the Medical Society of Göteborg.

Accepted for publication March 29, 1991.

Address correspondence to Dr. Kirnö, Department of Anesthesia and Intensive Care, Sahlgren's Hospital, S-413 45 Göteborg, Sweden.

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0003-2999/91/$3.50

the GSR. Therefore, we have also used the intraneural stimulation model for quantitative pharmacologic analysis of the effect of systemically (intravenously) administered atropine on the GSR amplitude.

Methods

Experiments were performed on 15 healthy subjects, aged 21–49 yr. Written informed consent was given by all subjects and the investigation was approved by the Human Ethics Committee, University of Göteborg.

With the subjects in the supine position, a plastic cannula (Contiplex, B. Braun Melsungen AG, Germany), to be used for injection of a local anesthetic, was inserted into the left axilla and was placed within the sheath surrounding the axillary artery and nerves. The correct position of the cannula was verified by injection of a few milliliters of cold saline solution that evoked short-lasting but distinct paresthesias in the hand. Subsequently, a tungsten microelectrode with a tip diameter of a few microns was inserted into the median nerve 2–3 cm proximal to the wrist, and a similar reference electrode was placed subcutaneously a few centimeters away. A nerve fascicle innervating the index or the middle finger (and occasionally, part of the palm) was impaled. The area innervated by the fascicle was outlined by evoking afferent mechanoreceptor discharge through stroking the skin. Within this area, two Ag-AgCl electrodes (Medicotest A/S, Denmark) were applied. Skin resistance between these electrodes was recorded using a Van Gogh galvanic skin reflex module (type IGSR-ZA) with a rise time constant of 0.3 s and a decay time constant of 3 s. The measuring current was 12 μA, and the signal was passed through two separate filters. The direct current (DC) registration (no low-cut filter) expressed the absolute skin resistance level and the alternating current (AC) registration (0.7 Hz, low-cut filter) represented the change of skin resistance. In three experiments in which sweat production was recorded as water vapor partial pressure with an Evaporimeter EP1 (Servo Med AB, Stockholm, Sweden), the evaporimeter and GSR probes were placed close to each other within the innervation zone. An electrocardiogram was recorded by surface electrodes on the chest.

With all electrodes in place, axillary nerve blockade was induced by injection of 30–35 mL of mepivacaine (Carbocain, 10 mg/mL, Astra, Sweden), into the axillar cannula. The experiments demanded full anesthetic effect and complete inhibition of spontaneous GSR as well as of GSR evoked by sudden unexpected sounds or touches proximal to the blockade (arousal stimuli). This was usually achieved within 30–40 min. To ensure complete nerve blockade throughout the whole experiment, an additional injection of 10 mL of mepivacaine was given after 1–1.5 h. For intraneural stimulation, a Grass S48 stimulator (0.3-mA constant current, 0.2-ms duration) was used.

Continuous stimulation of the peripheral median nerve with single impulses at successively increasing frequencies (0.05, 0.1, 0.2, 0.5, 1, 2, 5, 10, 20 Hz) was delivered until at each frequency an approximate steady skin resistance level was reached. To compare GSRs following "bursts" of nerve traffic at different background levels of activity, identical trains of six impulses at 20 Hz were added to the background frequency at each steady state level.

In six experiments (subject weight, 50–66 kg), trains of six impulses at 20 Hz were delivered repetitiously at 0.1 Hz while atropine (Atropin 0.5 mg/mL, ACO, Sweden) was injected intravenously in incremental doses (0.01 mg–0.16 mg). After several minutes of steady-state train stimulation, the mean value of the amplitudes of the last 12 AC-GSRs preceding the first atropine injection was taken as reference (100%). Subsequently, the mean value of the last three amplitudes in each dose interval (2 min) was used in a dose-response plot. In two subjects, the ability of atropine to abolish GSR to arousal-induced sympathetic nerve discharge in the nonanesthetized contralateral hand was evaluated.

Results

The DC-GSR recordings consistently showed stepwise decreased skin resistance with increasing background stimulation frequency ($n = 6$). A typical experiment is shown in Figure 1. In all subjects, the train-induced GSR amplitude (both AC and DC) varied in a nonlinear fashion with the background frequency, reaching a maximum at 0.5 Hz in two subjects, at 0.2 Hz in three subjects, and at 0.1 Hz in one subject (Figure 2). At the higher background frequencies (>5 Hz), the DC resistance level was low and the train stimuli caused little or no further reduction. Potentiation of the AC-GSR amplitudes to the first few background stimuli after the train stimulation was observed at the lower frequencies. This was less pronounced at background frequencies above 0.5 Hz and absent above 2 Hz.

In three subjects, sweat production was monitored concomitantly with the skin resistance level during stimulation with stepwise increasing frequencies. These experiments demonstrated a consistent frequency-response relationship with an essentially concomitant reduction in skin resistance and increase in sweat production (Figure 3).

The injection of atropine reduced GSRs to train

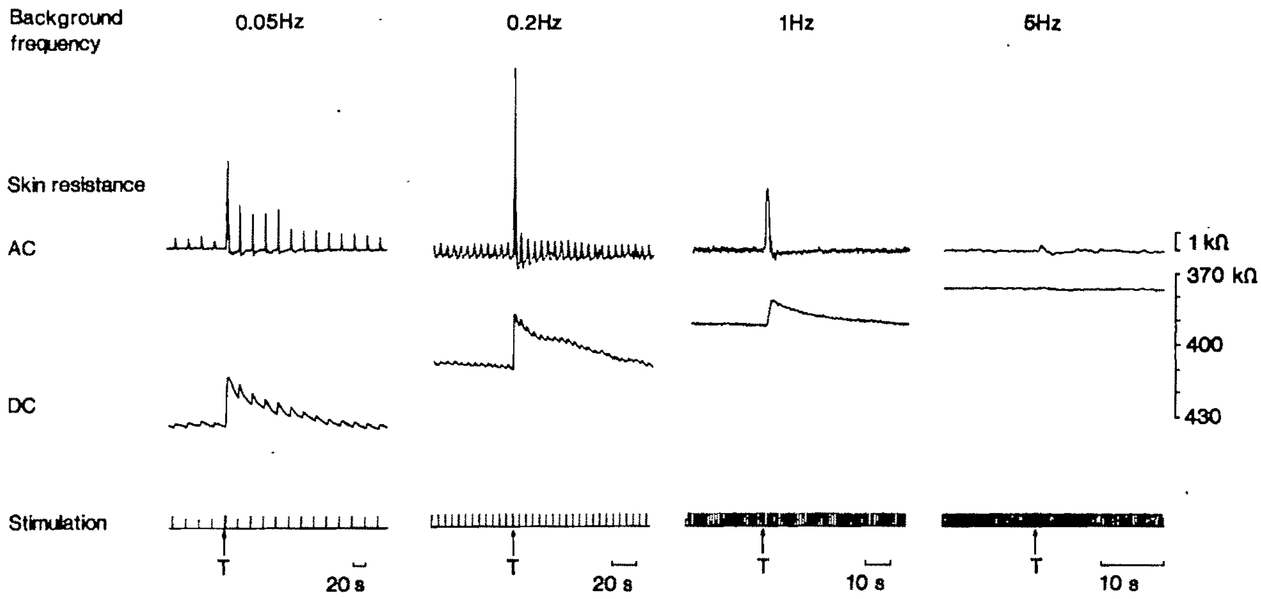

Figure 1. Effects of intraneural stimulation of a skin fascicle in the median nerve on skin resistance within the area of innervation in the index finger. At each background frequency a train (T) of six impulses at 20 Hz was added. In this subject, the maximum change in skin resistance (AC) occurred at a background frequency of 0.2 Hz. Note the potentiation (at 0.05 and 0.2 Hz) of skin resistance changes in response to the first few background stimuli succeeding the train.

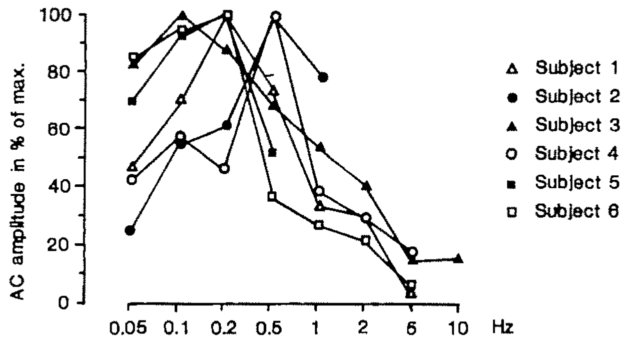

Figure 2. Train-induced changes in skin resistance (AC) at different background frequencies in six subjects. In each subject, the AC amplitude increased to a maximum (100%) and then decreased, indicating a nonlinear relationship with the background frequencies.

stimuli as shown in Figure 4A ($n = 6$). After each injection, a steady-state GSR amplitude was achieved after approximately 1 min. The response pattern to incremental doses of atropine was similar in all subjects despite the fact that the absolute GSR amplitudes before atropine injection varied markedly between subjects. By plotting the accumulated atropine dose and the AC-GSR amplitude, a dose-response curve was achieved (Figure 4B). In two subjects, a 0.5-mg dose of atropine reduced but did not abolish the arousal-induced GSR (see Methods) in the contralateral hand.

Discussion

Elimination of spontaneous sympathetic nerve activity in the hand by the use of an axillary blockade offers an experimental model for studying effector responses to a controlled sympathetic sudomotor nerve traffic evoked by intraneural electrical stimulation. The stimulation-induced decreases in skin resistance and increases in water vapor partial pressure demonstrate the close relationship between sweat production and skin resistance level (Figure 3). The model also enables pharmacologic evaluation of the sensitivity of human eccrine sweat glands to different drugs under standardized conditions.

Our main finding was a nonlinear relationship between the background frequency and the train-induced GSR amplitude in the lower background frequency range. At high frequencies (>5 Hz), the addition of a train of stimuli caused little or no change in skin resistance, probably because the sweat glands were more or less maximally activated by the background stimulation itself. Furthermore, the contrast between the train (20 Hz) and the background frequency was less pronounced. The potentiation of GSR immediately following a train stimulus, seen at the lower background frequencies, is in agreement with an earlier study by Wallin et al. (11) who found that the reduction in skin resistance seen after a stimulus depended on whether previous stimuli had been given, on the number of stimuli given, and on the time elapsed from the last preceding stimulus. Consequently, the GSR to a single stimulus depends

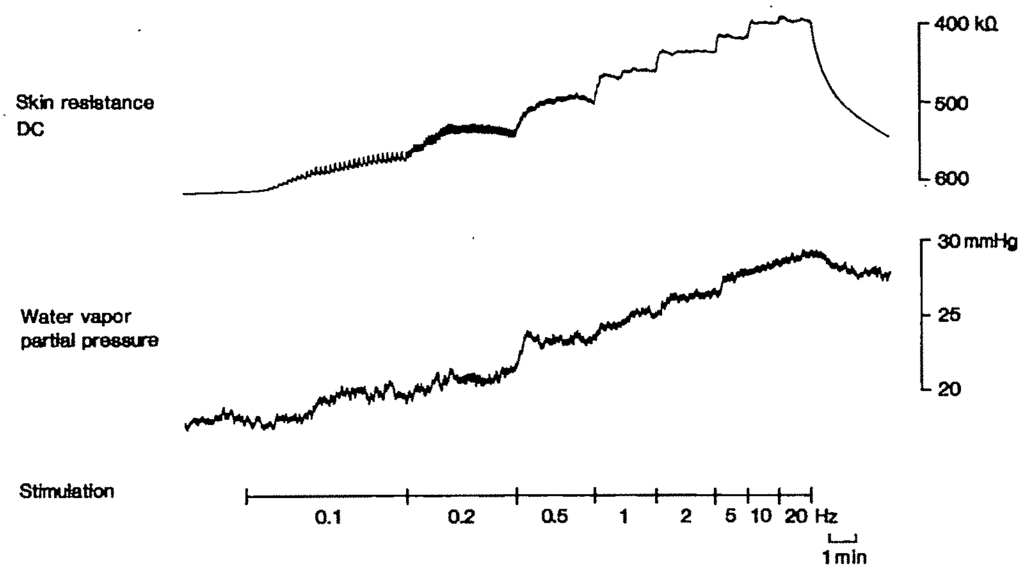

Figure 3. Effects of stepwise increased stimulation frequency on simultaneously recorded skin resistance and partial pressure of water vapor in one subject. With increased stimulation frequency, less time was needed to obtain a steady-state skin resistance level. Note the close relationship between increased evaporation and reduction of skin resistance.

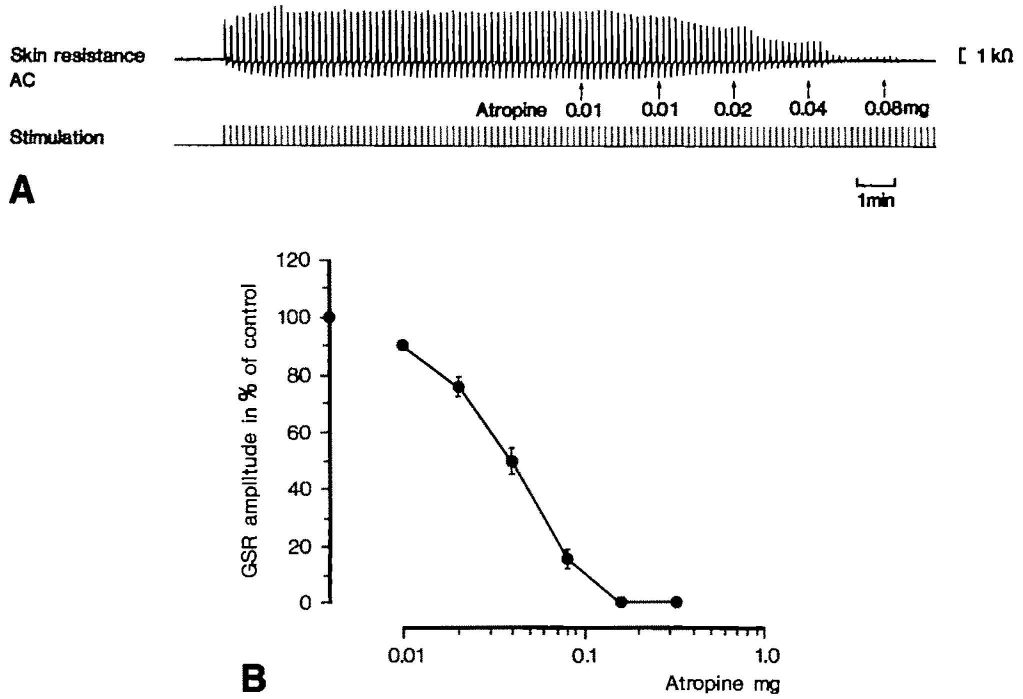

Figure 4. A. Recording of changes in skin resistance (AC) in response to train stimuli (six impulses at 20 Hz) delivered every 10 s. Atropine given intravenously in incremental doses abolished GSR at a cumulative dose of 0.16 mg. **B.** Dose-response curve showing the effect of atropine given intravenously on changes of skin resistance (AC) in response to train stimuli in six subjects (mean ± SEM). Note the small SEM values, illustrating the consistency of the atropine-induced changes in sudomotor function.

on the amount of sympathetic activity preceding the stimulus. This leads to the important conclusion that GSR amplitudes do not provide reliable estimates of the level of, or even direction of changes of, sympathetic nerve activity. High-amplitude GSRs during regression of regional blockades have been described in several studies (8,10, see introduction) and have been suggested to be the result of sympathetic activation in response to surgical trauma and other stress factors (8). This explanation seems unlikely, however, as the phenomenon also is present in relaxed volunteers who are not operated on (10). Another alternative seems more plausible. During regression of regional anesthesia, some sudomotor fibers will still be blocked, and therefore, fewer sympathetic impulses will reach the sweat glands than in the control situation before the nerve blockade. As the results of the present study show, this could well explain why GSR amplitudes following bursts of nerve impulses are higher during regression of nerve blockade.

The results obtained after intravenous injection of atropine confirm that human sweat glands are innervated primarily by cholinergic fibers (12) and that GSR is very sensitive to anticholinergic drugs. The accumulated dose necessary for total abolition of GSR in the intraneurally stimulated skin area was low (0.16 mg). In line with earlier findings (13), a 0.5-mg dose of atropine was necessary to markedly reduce the GSR in the contralateral unblocked hand produced by arousal stimuli (see Methods). One reason for this discrepancy between the blocked and the unblocked hand may be that not all sudomotor fibers in the impaled fascicle were stimulated. However, preliminary experiments with varying stimulation currents make this explanation less likely. Second, the stimulation pattern could be important. Nilsson et al. (14) showed in a study on vasomotor function in rats that a higher degree of vasoconstriction in mesenteric arteries was evoked by irregular compared with regular stimulation. Whether irregular stimulation induces higher sweat production in humans, and therefore demands a larger dose of atropine for blocking, is not known. A third possibility is that fibers from different fascicles converge on the same skin area. If so, electrical stimulation of only one nerve fascicle would lead to submaximal activation of the sweat glands within a given skin area, which could explain why the stimulation-induced response was abolished by a low dose of atropine. The atropine dose-response curves were virtually identical in all subjects. Thus, the experimental model provides a sensitive cholinergic receptor assay as even a small shift of the atropine curve would disclose cholinergic receptor affinity of simultaneously present drugs.

In conclusion, this study demonstrates that GSR does not provide a quantitative estimate of either level or direction of changes of sympathetic nerve activity. Therefore, it cannot be used to evaluate the completeness of sympathetic blockade in regional anesthesia. On the other hand, GSR correlates closely with sweat production. Thus, the relationship between skin sympathetic nerve activity and sweat production is a complex nonlinear function.

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Cardiovascular Actions of Desflurane in Normocarbic Volunteers

Richard B. Weiskopf, MD, Michael K. Cahalan, MD, Edmond I. Eger II, MD,
Nobuhiko Yasuda, MD, Ira J. Rampil, MD, Pompiliu Ionescu, MD,
Stephen H. Lockhart, PhD, MD, Brynte H. Johnson, MS, Beth Freire, BS,
and Scott Kelley, MD

Departments of Anesthesia and Physiology and the Cardiovascular Research Institute, University of California, San Francisco, California

The cardiovascular actions of three concentrations of desflurane (formerly I-653), a new inhalation anesthetic, were examined in 12 unmedicated normocapnic, normothermic male volunteers. We compared the effects of 0.83, 1.24, and 1.66 MAC desflurane with measurements obtained while the same men were conscious. Desflurane caused a dose-dependent increase in right-heart filling pressure and a decrease in systemic vascular resistance and mean systemic arterial blood pressure. As measured by echocardiography, left ventricular end-diastolic area did not change except for a small increase at 1.66 MAC desflurane, and systolic wall stress was less at all concentrations of desflurane than during the conscious state. Desflurane did not change cardiac index or left ventricular ejection fraction. Heart rate did not change at 0.83 MAC, but progressively increased with deeper desflurane anesthesia. Stroke volume index was less at all concentrations of desflurane than while the men were conscious, but desflurane did not alter the velocity of ventricular circumferential fiber shortening. Mixed venous blood Po_2 and oxyhemoglobin saturation were higher during all concentrations of desflurane anesthesia than during the conscious state. No volunteer developed a metabolic acidosis. We conclude that desflurane with controlled ventilation and constant $Paco_2$ causes cardiovascular depression, as indicated by the increased cardiac filling pressure and decreased stroke volume index and by no change in the velocity of circumferential fiber shortening in the presence of decreased systolic wall stress. However, cardiac output is well maintained, and heart rate does not increase at light levels of anesthesia. The cardiovascular actions of 0.83 and 1.66 MAC desflurane were also reexamined in 6 of the 12 men during the seventh hour of anesthesia. Prolonged desflurane anesthesia resulted in lesser cardiovascular depression than was evidenced during the first 90 min. The measures of cardiac filling (central venous pressure and left ventricular end-diastolic cross-sectional area) did not differ between the early and late periods of anesthesia. Systemic vascular resistance decreased further during the late period, but systolic wall stress did not differ between the two time periods. During the seventh hour of desflurane anesthesia, heart rate and cardiac index were higher at both anesthetic concentrations than during the first 90 min of anesthesia. Left ventricular ejection fraction and velocity of fiber shortening did not change with duration of desflurane anesthesia. Oxygen consumption, oxygen transport, the ratio of the two, mixed venous Po_2, and mixed venous oxyhemoglobin saturation (So_2) increased late in the anesthetic in comparison with the first 90 min.

(Anesth Analg 1991;73:143–56)

Desflurane (formerly I-653) is a new inhaled anesthetic, structurally similar to isoflurane, but with advantageous lower blood (1) and tissue (2) solubilities, and little or no metabolism (3–5). The cardiovascular effects of desflurane in swine do not differ from those of isoflurane (6), nor does desflurane sensitize swine myocardium to exogenously administered epinephrine (7). These properties led us to evaluate the cardiovascular properties of desflurane, with and without nitrous oxide, in human volunteers not undergoing surgery. In this paper, we report our findings of the cardiovascular actions of desflurane in oxygen with ventilation controlled to maintain normocapnia. Because duration of halothane (8,9), fluroxene (10), and enflurane (11) anesthesia is associated with cardiovascular changes,

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Supported by the Anesthesia Research Foundation and a grant from Anaquest, Inc.

Accepted for publication April 4, 1991.

Address correspondence to Dr. Weiskopf, Department of Anesthesia, University of California, San Francisco, CA 94143-0648.

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0003-2999/91/$3.50

Table 1. Physical Characteristics and Baseline Values of Volunteers

	All volunteers (n = 12)	Volunteers given desflurane in O$_2$ first (n = 6)
Age (yr)	23.8 ± 0.7	24.2 ± 0.9
Height (cm)	181 ± 2	182 ± 4
Weight (kg)	76 ± 5	76 ± 7
BSA (m^2)	2.0 ± 0.1	2.0 ± 0.1
Temperature (°C)	36.71 ± 0.07	36.70 ± 0.09
HR (beats/min)	70 ± 2	69 ± 2
MAP (mm Hg)	85 ± 3	81 ± 3
MPAP (mm Hg)	13.4 ± 0.9	13.3 ± 1.4
CVP (mm Hg)	5.0 ± 0.8	4.7 ± 1.0
CI (L·min^{-1}·m^{-2})	3.7 ± 0.1	3.65 ± 0.14
SVR (dyne·sec·cm^{-5})	901 ± 44	868 ± 35
SVI (mL/m^2)	53 ± 2	53.4 ± 2.3
LVEDA$_c$ (cm^2)	22.1 ± 0.9	22.5 ± 1.6
LVESA$_c$ (cm^2)	12.2 ± 0.8	12.2 ± 1.2
LVEF (%)	45.2 ± 2.6	46 ± 4
Vcfs (circ/s)	0.66 ± 0.05	0.67 ± 0.06
SWS (g/cm^2)	102 ± 9	106 ± 9
Pao$_2$ (mm Hg)	102 ± 2	102 ± 3
Paco$_2$ (mm Hg)	41.4 ± 0.7	42.5 ± 0.7
pHa (U)	7.419 ± 0.011	7.401 ± 0.004
Pvo$_2$ (mm Hg)	48.0 ± 0.9	48.6 ± 1.4
Svo$_2$ (%)	82.6 ± 0.8	82.6 ± 1.1
To$_2$ (mL O$_2$·min^{-1}·m^{-2})	17.8 ± 0.6	17.7 ± 0.6
Vo$_2$ (mL O$_2$·min^{-1}·m^{-2})	2.72 ± 0.11	2.69 ± 0.14
To$_2$/Vo$_2$	6.65 ± 0.37	6.65 ± 0.62
Base-excess (mEq/L)	1.9 ± 0.7	1.1 ± 0.3

BSA, body surface area; HR, heart rate; MAP, mean arterial blood pressure; MPAP, mean pulmonary arterial blood pressure; CVP, central venous pressure; CI, cardiac index; SVR, systemic vascular resistance; SVI, stroke volume index; LVEDA$_c$, left ventricular end-diastolic cross-sectional cavity area; LVESA$_c$, left ventricular systolic cross-sectional cavity area; LVEF, left ventricular ejection fraction; Vcfs, velocity of circumferential fiber shortening; SWS, systolic wall stress; Pao$_2$, arterial oxygen tension; Paco$_2$, arterial carbon dioxide tension; Pvo$_2$, mixed venous blood partial pressure of oxygen; Svo$_2$, mixed venous oxyhemoglobin saturation; To$_2$/Vo$_2$, ratio of oxygen transport to oxygen consumption.

Data are mean ± SE.

we also tested the hypothesis that the cardiovascular actions of desflurane during the seventh hour of anesthesia would not differ from those during the first 90 min.

Methods

These studies were performed with approval of the Committee on Human Research of the University of California, San Francisco, and with informed consent of the 12 healthy male volunteers (Table 1). Each subject had normal physical examination results, complete blood count, plasma alanine aminotransferase activity, plasma creatinine concentration, and urinalysis. None had a history of cardiovascular, pulmonary, or hepatic disease, general anesthesia within 6 mo of this study, medications within 7 days, alcohol for at least 2 days, or food or drink within 12 h of the study.

The morning of the study, after the volunteer rested quietly for 10–15 min, we obtained and recorded a short-axis two-dimensional echocardiogram (Hewlett-Packard, Andover, Mass.) of the left ventricle at the mid-papillary muscle level by placing a transducer over the volunteer's left parasternal area, while he lay in the left lateral decubitus position. With the volunteer supine, after infiltration with 1% xylocaine, cannulas were placed in a vein of the upper extremity, a radial artery, and the pulmonary artery via the right internal jugular vein. Position of the triple-lumen, thermodilution pulmonary artery catheter was verified by the pressure wave form. The cannula was positioned with the distal orifice in the pulmonary artery and the proximal orifice in a central vein as determined by the pressure tracing. The radial artery cannula and both lumena of the pulmonary artery cannula were connected to Gould Statham 23XL transducers, and the pressures were continuously recorded using a digital polygraph (Gould model ES 2000). Zero pressure was adjusted relative to the mid-axillary line before each measurement. At the start and end of each study, transducer gain was checked with a mercury manometer. The electrical activity of lead II of the electrocardiogram was continuously recorded. Cardiac ouput was determined in duplicate by thermodilution, injecting 10 mL of 0°C saline into the right atrium at end-expiration (Edwards model 9100A analog computer). The injectate temperature was continuously measured (American Edwards part 93-510) and the wash-out curve was recorded and inspected to confirm that it was exponential. If the two determinations of cardiac output differed by more than 10%, a third or, if necessary, a fourth determination was made. The pulmonary artery thermister was used to measure body temperature, which was maintained throughout the study (36.8 ± 0.0°C) at values not different from conscious values with a forced-air warming device (Bair Hugger, Augustine Medical Inc; Eden Prairie, Minn.). Change in calf circumference during venous occlusion was determined using a Whitney strain gauge, and blood flow (muscle) was calculated. During each study condition, systemic arterial (radial) and mixed venous (pulmonary arterial) Po$_2$, Pco$_2$, and pH were measured with standard electrodes (Radiometer model ABL2 automated blood gas analyzer). Throughout the study, the concentrations of carbon dioxide and desflurane were measured continuously by infrared spectrometry (modified Datex model 254) at the mouth (conscious) or endotracheal tube orifice (anesthetized) and recorded. The infrared analyzer was calibrated with secondary (tank) standards of desflurane, which were analyzed by gas chromatographs calibrated with primary (flask) standards.

After a minimum of 15 min of stable (<10% variation) heart rate, systemic and pulmonic arterial systolic and mean blood pressures, and cardiac output, cardiovascular measurements were made while the subject was conscious and supine breathing air. Pulmonary arteriolar occlusion pressure was not measured for reasons of safety.

Anesthesia was then induced via a mask with desflurane in oxygen, and the trachea was intubated without the use of additional drugs. Ventilation was mechanically controlled to maintain arterial Pco_2 close to that in the conscious volunteer. A transesophageal echocardiographic transducer was then passed into the esophagus and positioned to obtain a short-axis cross-sectional view similar to that recorded before induction of anesthesia.

Volunteers were assigned randomly to receive first either desflurane in oxygen or desflurane in 60% nitrous oxide, balance oxygen. The results of the cardiovascular measurements during desflurane in nitrous oxide are reported in a companion manuscript (12). Cardiovascular measurements were obtained after 12 min of stable end-tidal anesthetic concentrations of (6%, 9%, and 12% desflurane in oxygen and 3%, 6%, and 9% desflurane in nitrous oxide). The two lower concentrations were administered in random order, and the highest, for safety, was always administered last. After measurements were complete, the background gas was switched (i.e., for those given oxygen alone, it was changed to nitrous oxide plus oxygen and the reverse in the other six subjects) and the measurements were repeated at the three anesthetic concentrations. When we initiated these studies, preliminary data indicated a value of 6% desflurane as MAC. Rampil et al. (13) subsequently determined MAC for desflurane in this age group to be 7.25%. Thus, although we had intended to perform these studies at 1, 1.5, and 2 MAC, they were performed at 0.83, 1.24, and 1.66 MAC.

During each study condition (conscious and three levels of anesthesia), we also computed the following variables: cardiac index, $Q_tI = Q_t/BSA$; stroke volume index, $SVI = Q_tI/HR$; systemic vascular resistance, $SVR = (MAP - CVP)/Q_t$; oxygen content of arterial (Cao_2) and mixed venous (Cvo_2) blood; oxygen consumption, $Vo_2 = 10(Cao_2 - Cvo_2)(Q_t)/Wt$; and oxygen transport, $To_2 = 10(Cao_2)(Q_t)/Wt$; where Q_t is cardiac output, BSA is body surface area (14), HR is heart rate, MAP is mean systemic arterial blood pressure, CVP is central venous blood pressure, and Wt is body weight. Arterial blood base-excess was determined by computerized equations (15).

The echocardiograms were analyzed for segmental wall-motion changes (16). The following variables also were determined as described in an accompanying manuscript (12): left ventricular end-diastolic and end-systolic cross-sectional cavity areas (EDA_c and ESA_c) and circumferences (EDC_c and ESC_c), systolic wall stress (SWS), and velocity of circumferential fiber shortening corrected for heart rate (Vcfc).

To test for the influence of prolonged desflurane anesthesia, these measurements were repeated during the seventh hour of desflurane anesthesia, at 0.83 and 1.66 MAC desflurane, with the background gas used in the first 90 min of anesthesia. Thus, 6 of the 12 volunteers were studied during the seventh hour while anesthetized with desflurane in oxygen. In all cases, the end-tidal concentration of desflurane was maintained for 15 min before cardiovascular measurements. Between the first 90 min and the seventh hour of anesthesia, several studies were performed and are reported elsewhere (12,17–20). These included studies of the influence of the background gas, spontaneous ventilation, and hyperventilation. In all cases, anesthesia was maintained with no drugs other than desflurane with or without nitrous oxide, and the volunteer was maintained normothermic.

For each variable, we tested whether the order of administration of background gas or order of anesthetic concentration influenced the results using *t*-tests. With one exception (see below) we found no such influences and, therefore, we pooled the data for like conditions. The pooled values for each variable during each study condition were compared by analysis of variance with repeated measures, and Newman-Keul's method of multiple comparison (21).

The cardiovascular effects of desflurane in oxygen and in nitrous oxide and oxygen during the seventh hour of anesthesia were compared separately with the data from the conscious volunteers by analysis of variance with repeated measures and Newman-Keul's method of multiple comparisons (21). Data from the first 90 min (early) and seventh hour (late) of desflurane anesthesia were compared separately for each background gas using paired *t*-tests. Data obtained during the late period was also tested for the effect of background gas (O_2 vs N_2O in O_2) by unpaired *t*-test.

In all cases, statistical significance was accepted at $P < 0.05$.

Results

The First 90 Minutes of Anesthesia

The order of administration of anesthetic concentration did not influence the results and the data for a given concentration are therefore pooled. Similarly, except for heart rate, the order of administration of

Table 2. Temperature and Arterial Blood Gas Tensions During Desflurane Anesthesia

	Desflurane concentration (MAC)			
	0	0.83	1.24	1.66
Temperature (°C)	36.71 ± 0.07	36.68 ± 0.06	36.77 ± 0.06	36.77 ± 0.05
$Paco_2$ (mm Hg)	41.4 ± 0.7	38.1 ± 0.8[a]	37.5 ± 0.6[a]	37.5 ± 0.7[a]
Pao_2 (mm Hg)	102 ± 2	486 ± 14[a]	472 ± 12[a]	459 ± 14[a]
pH (U)	7.419 ± 0.011	7.424 ± 0.012	7.439 ± 0.11	7.428 ± 0.012
Base-excess (mEq/L)	1.9 ± 0.7	0.6 ± 0.6	0.7 ± 0.5	0.7 ± 0.6

$Paco_2$, arterial carbon dioxide tension; Pao_2, arterial oxygen tension.
Data are mean ± SE.
[a] Significantly different ($P < 0.05$) from conscious (0 MAC) value.

background gas did not significantly alter the cardiovascular data obtained when desflurane was given in oxygen alone. Therefore, all results are pooled, except for those of heart rate. The six subjects given desflurane in oxygen first were demographically similar to the entire group: age, 23 ± 0.7 yr; weight, 76.4 ± 4.7 kg (mean ± SE). Pulmonary arterial blood temperature and arterial pH were maintained unchanged throughout the study (Table 2). Arterial Pco_2 was significantly lower (38 mm Hg) during desflurane anesthesia than during the conscious state (41 mm Hg, Table 2); however, this small difference is not physiologically important.

Desflurane caused a dose-dependent increase in right-heart filling pressure (Figure 1) and a decrease in systemic vascular resistance (Figure 1) and mean systemic arterial blood pressure (Figure 2). Left ventricular end-diastolic area did not change at 0.83 or 1.24 MAC desflurane and increased by less than 10% at 1.66 MAC (Figure 1). Systolic wall stress was less at all concentrations of desflurane than when the volunteers were conscious, but did not differ among desflurane concentrations (Figure 1). Desflurane did not alter cardiac index, left ventricular ejection fraction, or calf muscle blood flow (Figure 2). In the six subjects given desflurane in oxygen first, heart rate did not change at 0.83 MAC (73 ± 2 beats/min vs 69 ± 2 beats/min conscious) but progressively increased with greater concentrations of desflurane (Figure 2). Subjects given desflurane in oxygen after desflurane in nitrous oxide had higher heart rates ($P < 0.05$) when given 0.83 MAC (84 ± 2 beats/min) or 1.24 MAC (87 ± 2 beats/min) desflurane in oxygen than those subjects first given desflurane in oxygen (Figure 3). Had we combined data for all 12 subjects, heart rate would have shown a dose-dependent increase with desflurane in oxygen. Stroke volume index was less during anesthesia at all concentrations of desflurane than when the subjects were conscious but did not differ among concentrations (Figure 2).

Despite dose-dependent increases in cardiac filling pressures, left-ventricular end-diastolic area did not change from the conscious value until 1.66 MAC was reached, and even then the increase was slight (9%) (Figure 1). The velocity of left ventricular circumferential fiber shortening was less at 1.66 MAC than at 0.83 MAC desflurane, but none of these values differed from the conscious values (Figure 1). No left ventricular segmental wall-motion abnormalities or ST-segment changes developed during the study. Mean pulmonary arterial blood pressure did not change at 0.83 and 1.24 MAC, but increased at 1.66 MAC (Figure 2). We did not compute pulmonary vascular resistance because we did not measure "wedge" or left atrial pressure. However, judging from the measured similar increases in mean and diastolic pulmonary arterial pressures and central venous pressure, and lack of change in cardiac output, it appears likely that pulmonary vascular resistance changed little, if at all. Oxygen transport, oxygen consumption, and the ratio of the two did not differ among concentrations of desflurane or from the conscious values (Figure 4). Mixed venous blood Po_2 and Svo_2 were higher during all concentrations of desflurane anesthesia than when the subjects were conscious, but did not differ among the concentrations of desflurane (Figure 4).

The Seventh Hour of Anesthesia

In general, compared with the first 90 min of desflurane anesthesia, the limited cardiovascular changes in the seventh hour of desflurane anesthesia were those of modest stimulation. The measures of cardiac filling (central venous pressure and left ventricular cross-sectional area) did not differ between early and late anesthesia at either 0.83 or 1.66 MAC desflurane (Figure 5). Systemic vascular resistance decreased further during the late period at 0.83 MAC but not at 1.66 MAC desflurane. Systolic wall stress did not differ between early and late anesthesia (Figure 5), but heart rate (Figure 6) and cardiac index (Figure 5) were higher after prolonged anesthetic exposure at both anesthetic concentrations than during the first hour of anesthesia. Stroke volume index (Figure 6), left ventricular ejection fraction (Figure 6), and veloc-

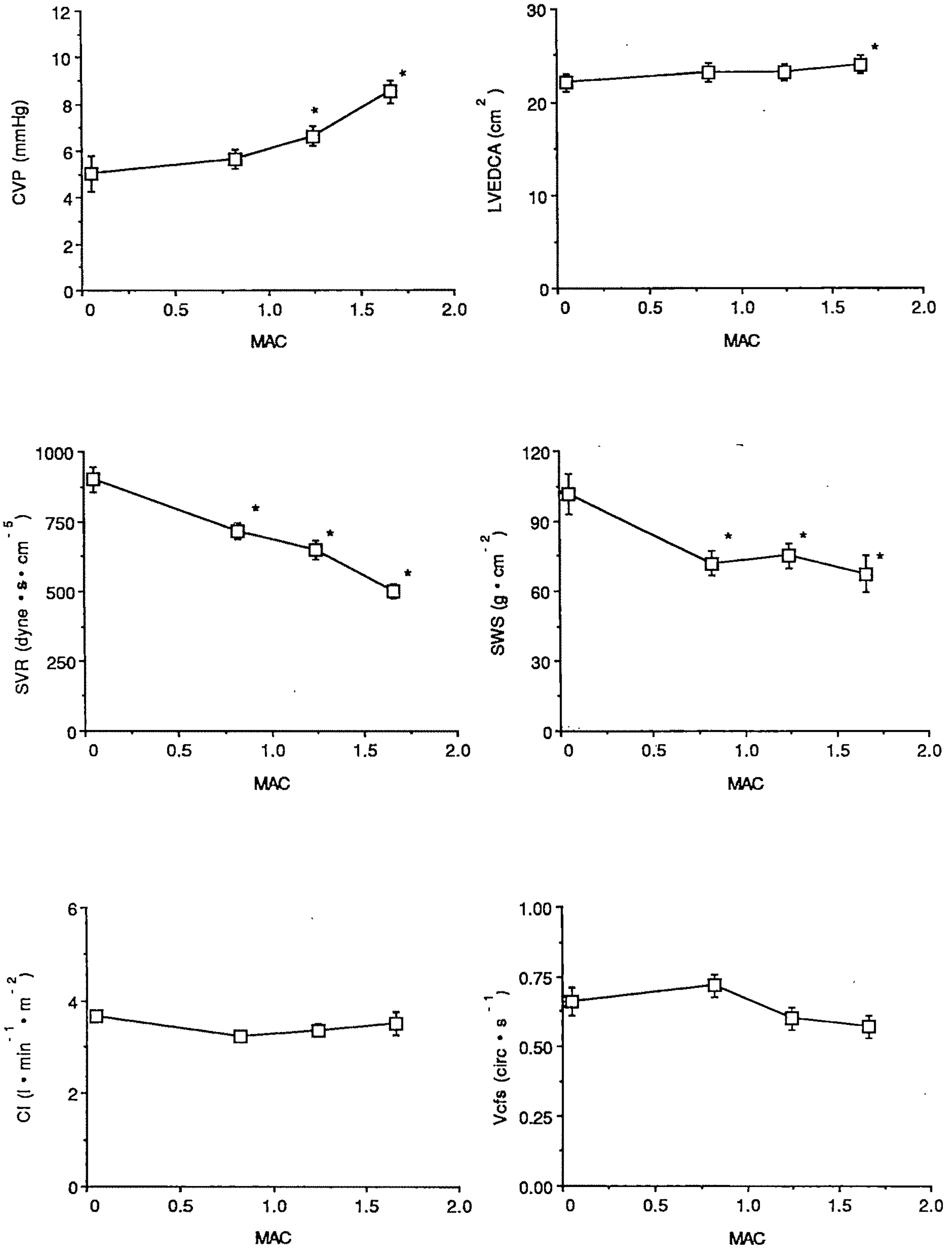

Figure 1. Central venous pressure (CVP), systemic vascular resistance (SVR), cardiac index (CI), left ventricular end-diastolic area (LVEDCA), left ventricular systolic wall stress (SWS), and left ventricular velocity of circumferential fiber shortening (Vcfs) in healthy men, conscious (0 MAC) and during three steady-state concentrations of desflurane anesthesia in oxygen with controlled ventilation. Values are mean ± SE. *$P < 0.05$ vs conscious value. $n = 12$.

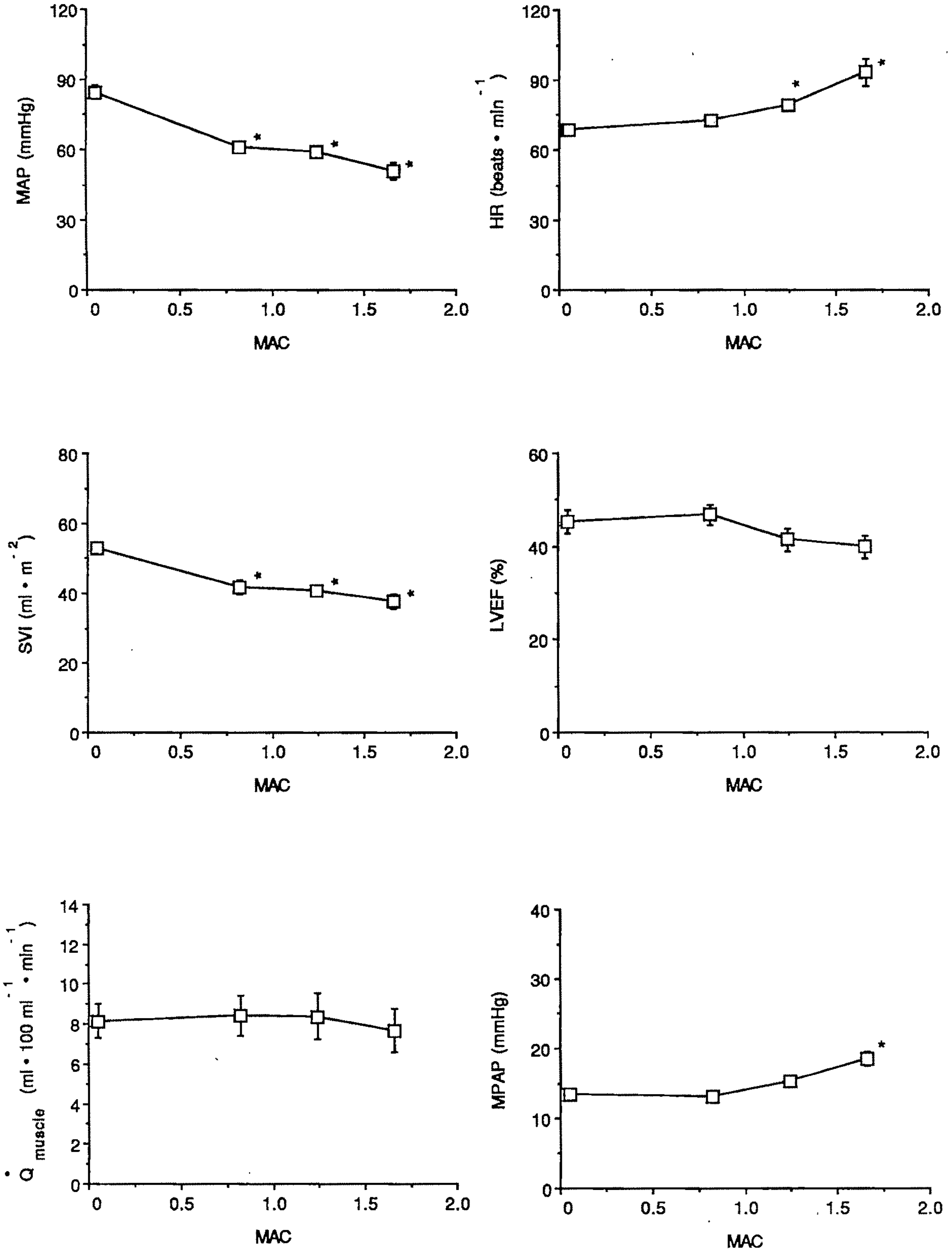

Figure 2. Mean arterial blood pressure (MAP), stroke volume index (SVI), muscle blood flow ($\dot{Q}_{muscle}$), heart rate (HR), left ventricular ejection fraction (LVEF), and mean pulmonary arterial blood pressure (MPAP) in healthy men, conscious (0 MAC) and during three steady-state concentrations of desflurane anesthesia in oxygen with controlled ventilation. *$P < 0.05$ vs conscious value. $n = 12$, except for heart rate, where $n = 6$ (see text).

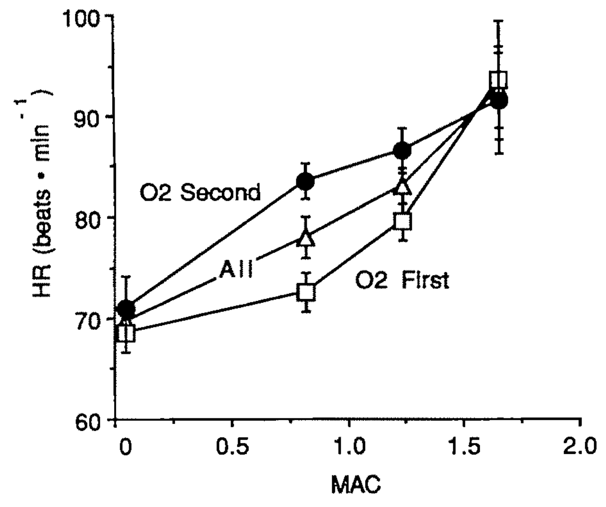

Figure 3. Heart rate in all 12 healthy volunteers during administration of desflurane in oxygen (△), and in the six volunteers who received desflurane in oxygen before (□) and in the six volunteers who received desflurane in oxygen after (●) receiving desflurane in nitrous oxide and oxygen.

ity of ventricular fiber shortening (Figure 5) and muscle blood flow (Figure 6) did not change during the late period at both anesthetic concentrations.

Oxygen consumption increased in the late period with both anesthetic concentrations (Figure 7), while oxygen transport increased during late anesthesia at 0.83 MAC. The ratio of oxygen transport to consumption, mixed venous $\mathrm{Po_2}$ and oxyhemoglobin saturation increased after prolonged anesthetic exposure at the lower (0.83 MAC) concentration (Figure 7). All other variables did not differ between the early and late periods at similar desflurane concentrations.

Discussion

All modern halogenated inhaled anesthetics depress myocardial contractility and cardiovascular function (8,11,22,23). We previously found in swine that the cardiovascular actions of desflurane are indistinguishable from those of isoflurane (6). We now report that in healthy human volunteers, desflurane, like isoflurane (22), decreases systemic vascular resistance and mean arterial blood pressure (Figure 8). Unlike other inhaled halogenated anesthetics (8,11,22,23), desflurane did not alter cardiac index, even with deep levels of anesthesia (1.66 MAC) (Figure 8). Unlike isoflurane, the maintenance of cardiac index at light levels of desflurane anesthesia is not dependent on increased heart rate; but at deeper levels of desflurane anesthesia, increased heart rate could have contributed to the maintenance of cardiac index.

The unchanged cardiac output in the presence of increased right-heart filling pressure, decreased systemic vascular resistance, and increased heart rate, suggests that desflurane decreases myocardial contractility, although probably less than that produced by other halogenated anesthetics (8,11,22,23; Figure 9). Decreased contractility also is implied by unchanged left ventricular circumferential fiber shortening at 1.24 and 1.66 MAC in the presence of unchanged end-diastolic area (and thus probably volume and preload) and decreased systolic wall stress (afterload). Despite increasing right-heart filling pressure, left ventricular end-diastolic area (and thus likely volume) did not change at 0.83 and 1.24 MAC and increased slightly at 1.66 MAC. In swine anesthetized with desflurane, right- and left-heart filling pressures change similarly (6). Therefore, it seems likely that in our subjects, left-heart filling pressures increased with increasing concentrations of desflurane, whereas left-ventricular end-diastolic volume did not. Consequently, decreased myocardial compliance may have played a role in the decreasing myocardial function in our subjects. Moores et al. described a similar effect of halothane in a swine right-heart bypass model (24). The greater increase in central venous pressure with desflurane than previously observed with isoflurane could have resulted from our volunteers receiving more intravenous fluid than the volunteers studied by Stevens et al. (22); alternatively, the relationship between ventricular pressure and volume was such that the changes in pressure were produced by only small changes in volume, which were difficult to detect by our methodology.

Desflurane did not change muscle blood flow. In human volunteers, isoflurane increased forearm blood flow twofold, but the increase was not dose-dependent (22). The difference between these studies could reflect differences in actions of the two anesthetics. However, the similarity of the effects of desflurane and of isoflurane on systemic vascular resistance suggests other causal factors. The major difference between our results and those of Stevens et al. is that our value for muscle blood flow during the conscious state is three times that reported by Stevens et al. (22). This could have resulted from our use of a surface warming device while our volunteers were conscious; Stevens et al. did not warm their volunteers while awake. In addition, Stevens et al. (22) measured forearm blood flow, whereas we measured calf blood flow; however, this difference is less likely to have caused the observed differences.

At all concentrations of desflurane, mixed venous blood $\mathrm{Po_2}$ and $\mathrm{So_2}$ values exceeded those obtained in conscious subjects. We previously observed in swine anesthetized with desflurane or isoflurane that cardiovascular deterioration and lactic acidosis do not occur until values for $\mathrm{Pvo_2}$ and $\mathrm{Svo_2}$ decrease below

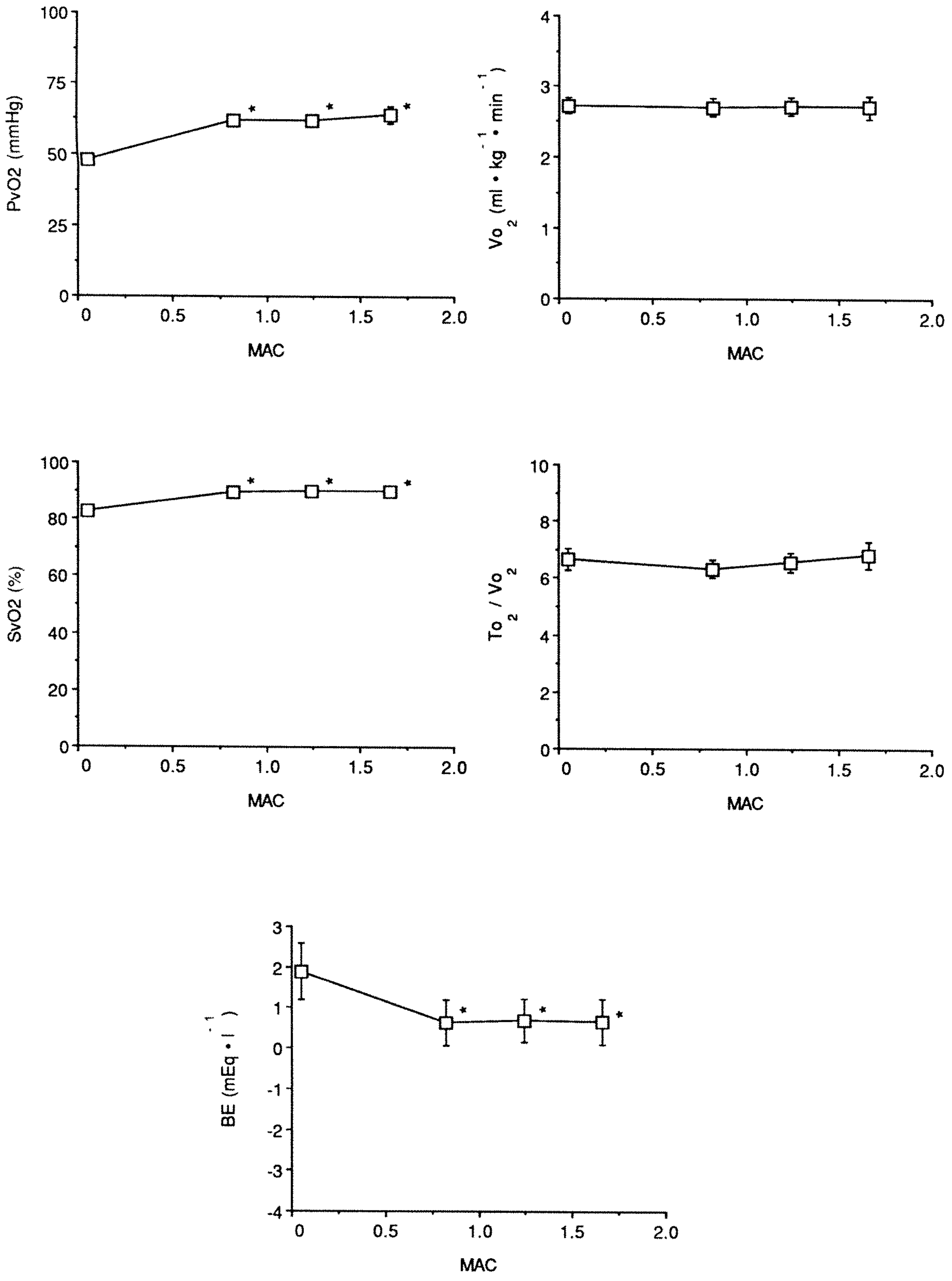

Figure 4. Mixed venous blood partial pressure of oxygen (Pvo_2), mixed venous oxyhemoglobin saturation (Svo_2), oxygen consumption (Vo_2), ratio of oxygen transport to oxygen consumption (To_2/Vo_2), and arterial blood base-excess (BE) in healthy men, conscious (0 MAC) and during three steady-state concentrations of desflurane anesthesia in oxygen with controlled ventilation. $*P < 0.05$ vs conscious value. $n = 12$.

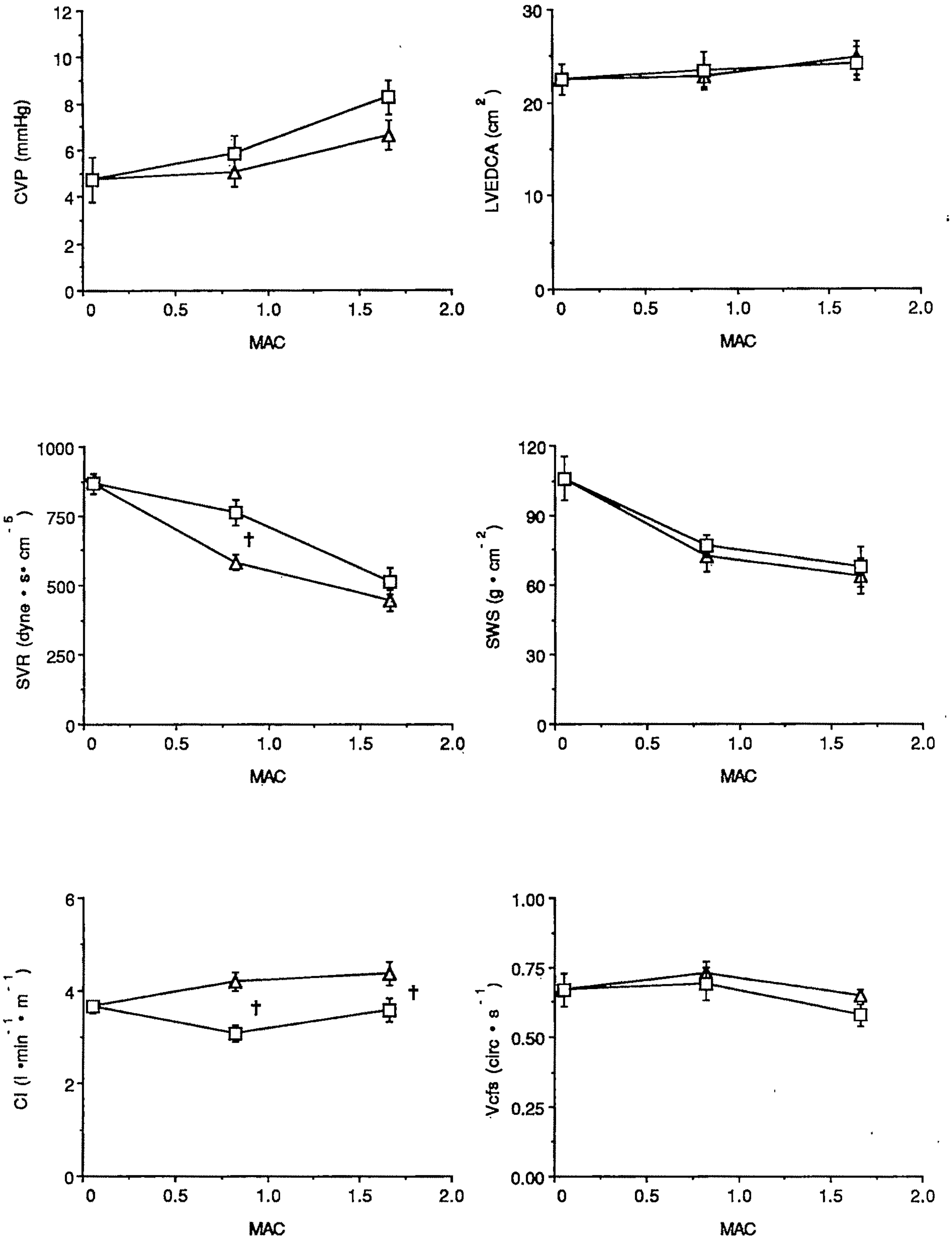

Figure 5. Central venous blood pressure (CVP), systemic vascular resistance (SVR), cardiac index (CI), left ventricular end-diastolic cross-sectional area (LVEDCA), left ventricular systolic wall stress (SWS), and velocity of left ventricular circumferential fiber shortening (Vcfs) in healthy men, conscious (0 MAC) and during the first 90 min (□) or seventh hour (△) of desflurane in oxygen anesthesia with controlled ventilation. †$P < 0.05$ early vs late. $n = 6$.

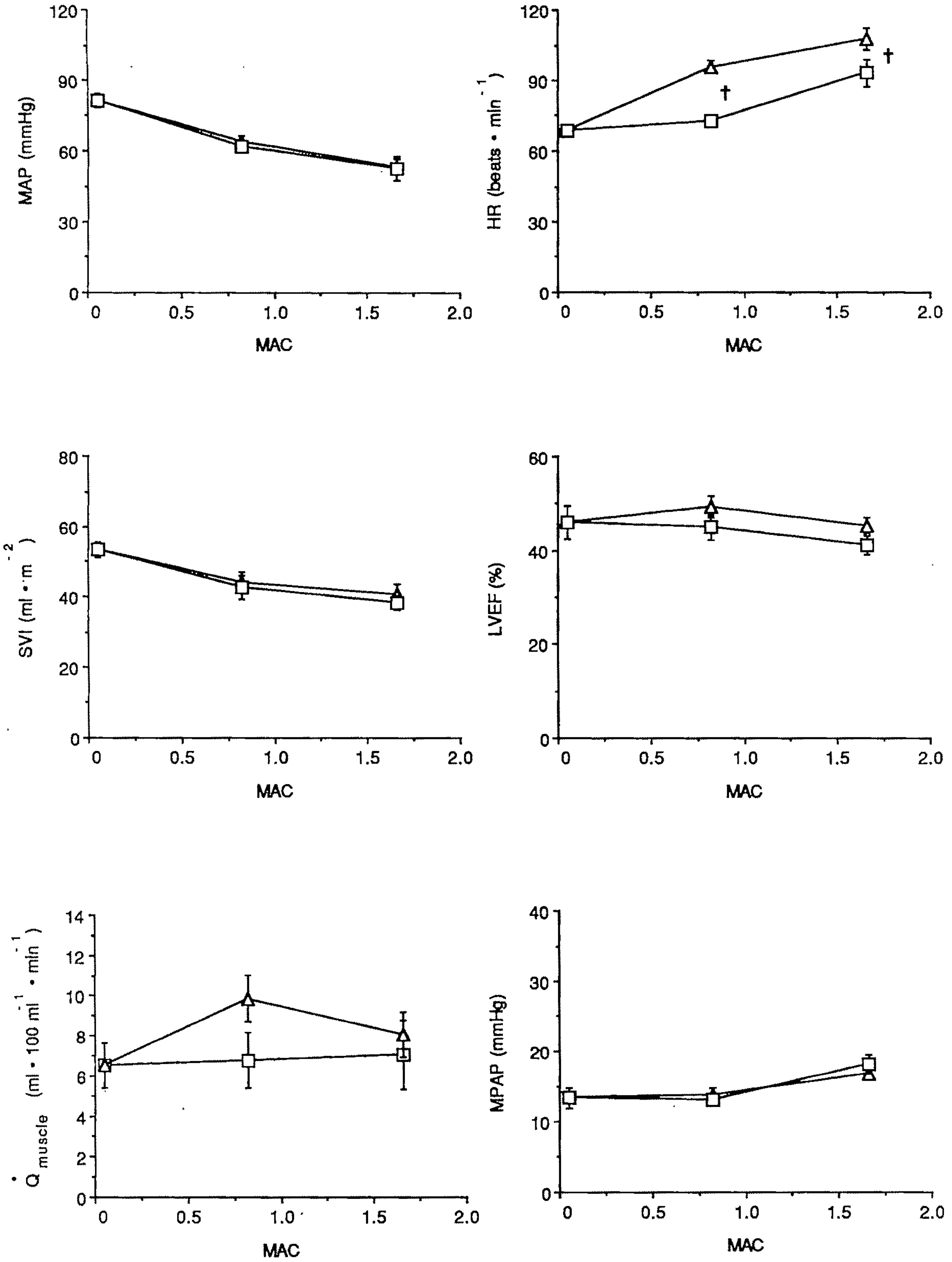

Figure 6. Mean arterial blood pressure (MAP), stroke volume index (SVI), muscle blood flow ($\dot{Q}_{muscle}$), heart rate (HR), left ventricular ejection fraction (LVEF), and mean pulmonary arterial blood pressure (MPAP) in healthy men, conscious (0 MAC) and during the first 90 min (□) or seventh hour (△) of desflurane in oxygen anesthesia with controlled ventilation. †$P < 0.05$ early vs late. $n = 6$.

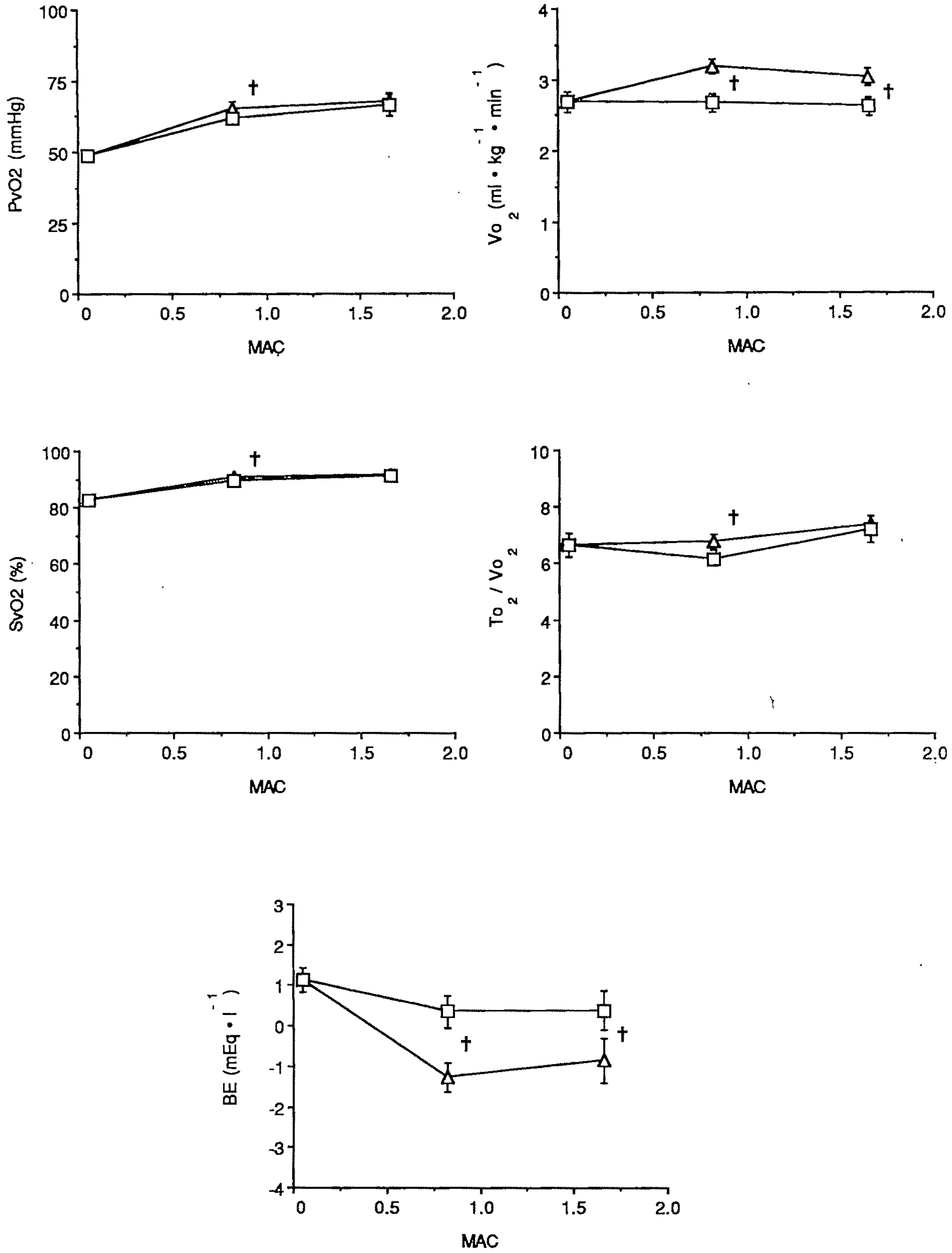

Figure 7. Mixed venous Po_2 (Pvo_2), mixed venous oxyhemoglobin saturation (Svo_2), oxygen consumption (Vo_2), ratio of oxygen transport to consumption (To_2/Vo_2), and arterial blood base-excess (BE) in healthy men, conscious (0 MAC) and during the first 90 min (□) or seventh hour (△) of desflurane in oxygen anesthesia with controlled ventilation. †$P < 0.05$ early vs late. $n = 6$.

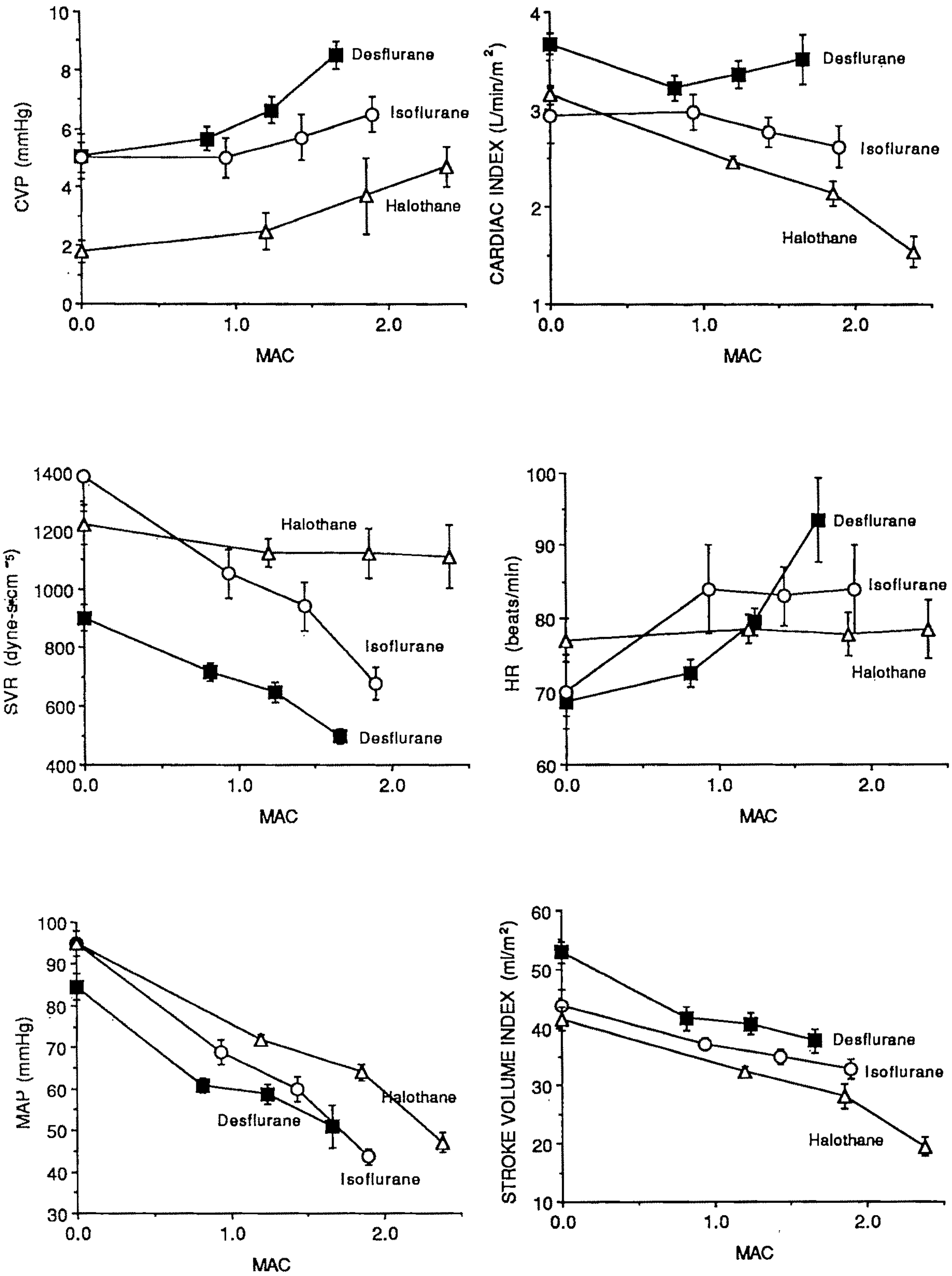

Figure 8. Comparison of the cardiovascular effects of desflurane (■) with those of isoflurane (○, from Reference 15) and halothane (△, from Reference 14) in healthy young men.

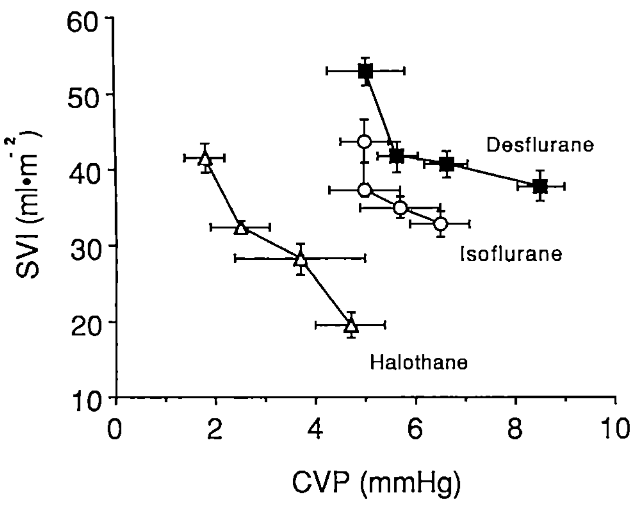

Figure 9. Comparison of stroke volume index (SVI) as a function of central venous pressure (CVP) during desflurane (■), isoflurane (O, Reference 15), and halothane (Δ, Reference 14) anesthesia in healthy young men.

those in conscious animals (25). These data and the lack of acidosis in our volunteers imply that despite the decrease in blood pressure produced by desflurane, tissue oxygen delivery remained satisfactory at all anesthetic levels.

Some of the cardiovascular depression observed during the first 90 min of anesthesia lessens or disappears after several hours of anesthesia with all inhaled halogenated anesthetics except isoflurane. Although desflurane is structurally similar to isoflurane, and its cardiovascular actions in swine (6) and humans (12) have many similarities to those of isoflurane, the cardiovascular changes we have observed with prolonged desflurane anesthesia more closely resemble those seen with halothane (8,9), enflurane (11), and fluroxene (10). These effects of duration are associated with a further decrease in systemic vascular resistance and a (consequent?) increase of cardiac index and heart rate. Cardiac output increased to values greater than those when the volunteers were conscious.

Price et al. (9) reported that administration of a β-sympathetic antagonist prevented changes seen with prolonged halothane anesthesia and accordingly attributed this recovery phenomenon to activation of β-sympathetic receptors. However, in his study (9) after 3 h, and in another study (8) after 5 h of halothane anesthesia, heart rate was not greater than during the first hour. Similarly, prolonged enflurane anesthesia (11) does not change heart rate despite decreased systemic vascular resistance and increased cardiac output, stroke volume, and dP/dt. The lack of change of muscle blood flow with prolonged desflurane anesthesia in oxygen also suggests the absence of β-sympathetic stimulation.

It has been suggested that the products of metabolic degradation may produce cardiovascular recovery with prolonged anesthesia (22). Evidence for this lies in the absence of stimulation and the minimal metabolism of isoflurane compared with the stimulation associated with prolonged anesthesia with halothane, enflurane, and fluroxene, which are metabolized to a greater extent than is isoflurane. Our data do not support this hypothesis. Desflurane undergoes little or no metabolism (3–5), is degraded 10- to 20-fold less than is isoflurane, yet demonstrates cardiovascular changes similar to those observed with halogenated anesthetics that are metabolized.

The "duration" portion of our study was designed to test the hypothesis that cardiovascular changes would not occur with prolonged desflurane anesthesia. Disproving this hypothesis, we have found that prolonged desflurane anesthesia does produce cardiovascular changes. The etiology of these changes remains unclear.

In summary, in young men desflurane anesthesia decreases systemic vascular resistance and mean arterial blood pressure and increases cardiac filling pressure. However, unlike results in swine, and unlike the effects of isoflurane in humans, light levels of desflurane anesthesia do not alter heart rate. Cardiac output and ventricular ejection fraction are well preserved at concentrations up to and including 1.66 MAC desflurane, and the decreased myocardial function appears to result from decreased contractility and perhaps decreased compliance. Prolonged desflurane anesthesia resulted in a modest lessening of cardiovascular depression.

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Hemodynamic Effects of Desflurane/Nitrous Oxide Anesthesia in Volunteers

Michael K. Cahalan, MD, Richard B. Weiskopf, MD, Edmond I. Eger II, MD,
Nobuhiko Yasuda, MD, Pompiliu Ionescu, MD, Ira J. Rampil, MD,
Stephen H. Lockhart, PhD, MD, Beth Freire, BS, and Natalie A. Peterson, BS

Departments of Anesthesia and Physiology, and the Cardiovascular Research Institute, University of California, San Francisco, California; Department of Anesthesiology, Jikei University School of Medicine, Tokyo, Japan

We determined the cardiovascular effects of 0.91, 1.34, and 1.74 MAC of desflurane/nitrous oxide anesthesia (60% inspired nitrous oxide contributed 0.5 MAC at each level) in 12 healthy, normocapnic male volunteers. Desflurane/nitrous oxide anesthesia decreased systemic blood pressures, cardiac index, stroke volume index, systemic vascular resistance, and left ventricular stroke work index, and increased pulmonary arterial pressures and central venous pressure in a dose-dependent fashion, while heart rate was 10%–12% and mixed venous oxygen tension was 2–4 mm Hg higher at all MAC levels than at baseline (awake). Desflurane/nitrous oxide anesthesia modestly increased left ventricular end-diastolic cross-sectional area (preload) and decreased velocity of left ventricular circumferential fiber shortening, systolic wall stress (afterload), and area ejection fraction; this combination of changes indicates myocardial depression. At approximately comparable MAC levels, heart rate was lower and systemic blood pressures, central venous pressure, left ventricular stroke work index, and systemic vascular resistance usually were significantly higher during anesthesia with desflurane and nitrous oxide than during desflurane anesthesia alone (same volunteers, data collected in crossover design). After 7 h of anesthesia, regardless of the background gas, somewhat less cardiovascular depression and/or modest stimulation was apparent: cardiac index, area ejection fraction, and velocity of left ventricular circumferential fiber shortening recovered to or toward awake values, whereas heart rate was further increased. Evidence of circulatory insufficiency did not develop in any volunteers during the study. Segmental left ventricular function was normal at baseline, and no segmental wall-motion abnormalities, ST-segment change, or dysrhythmias developed. We conclude that in healthy volunteers desflurane/nitrous oxide anesthesia is well tolerated and at approximately equal MAC levels causes somewhat less circulatory depression than desflurane anesthesia alone.

(Anesth Analg 1991;73:157–64)

Desflurane is a new inhalation anesthetic approved for experimental use in humans. It is a fluorinated methyl-ethyl ether identical to isoflurane in structure, except for the substitution of a fluorine for a chlorine atom on the α-methyl carbon. However, desflurane has a blood/gas solubility of 0.42 (1), which is less than one-third of isoflurane's value (1.4) and approximately equal to that of nitrous oxide (0.47). Like nitrous oxide, inspired and alveolar concentrations of desflurane equilibrate quickly, and after cessation of administration, both drugs are eliminated rapidly. However, the combined use of these agents should have significant advantages. For example, patients receiving 50%–60% nitrous oxide and desflurane should experience less hemodynamic depression than those anesthetized at a comparable depth with desflurane alone, because nitrous oxide is a less potent myocardial depressant and vasodilator (2) than desflurane (3,4). Accordingly, we designed the following study to determine the hemodynamic effects of desflurane and 60% nitrous oxide in healthy young volunteers not subjected to the confounding effects of other medications or surgery. Because some previous studies of inhaled agents have demonstrated attenuation of their cardiovascular effects with time (5–7), we continued anesthesia with desflurane for 7 h after which we repeated all cardiovascular measurements.

Supported by the Anesthesia Research Foundation and a grant from Anaquest, Inc. Dr. Eger and Dr. Cahalan are supported, in part, by grant 2P01AG03104-07 from the National Institutes of Health.

Accepted for publication April 4, 1991.

Address all correspondence to Dr. Cahalan, Department of Anesthesia, 521 Parnassus Avenue, Box 0648, Room C450, University of California, San Francisco, San Francisco, CA 94143-0648.

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0003-2999/91/$3.50

Methods

With approval from our committee on human research and informed consent from the volunteers, we studied 12 healthy young men (23.8 ± 2.5 yr). These volunteers were free of all systemic illness, took no medications or drugs, consumed less than 2 oz of alcohol per day, and did not smoke cigarettes.

The study was a crossover trial in which 12 volunteers received six treatments: 0.83, 1.24, and 1.66 MAC (minimum alveolar concentration) of desflurane alone, and 0.41, 0.84, and 1.24 MAC of desflurane plus 60% inspired nitrous oxide giving the combined values of 0.91, 1.34, and 1.74 MAC. The MAC of desflurane was assumed to be 7.25% (8) and 60% nitrous oxide was assumed to contribute 0.50 MAC. We designed the experiment to expose the volunteers to equipotent MAC levels of anesthesia with and without nitrous oxide, but we underestimated desflurane MAC by 10% (based on values known from limited human studies available at the time). By random assignment, six volunteers received the three concentrations of desflurane with nitrous oxide first, and the other six received it last. The order of study of MAC levels also was randomized, except for the highest MAC level, which we studied last in case the response at lower levels indicated that it probably would not be tolerated. However, all volunteers tolerated the 1.66 (desflurane) and 1.74 (desflurane plus nitrous oxide) MAC levels. In the six volunteers who received nitrous oxide first (during the initial 90 min of anesthesia), hemodynamics were reassessed at the 0.91 and 1.74 MAC levels of desflurane and nitrous oxide in the seventh hour of anesthesia. The intervening hours were used for studies of other effects of desflurane (9–12).

On arrival in the study room, volunteers were placed in the left lateral decubitus position on a padded operating room table. They rested quietly for 5–10 min while a left ventricular short-axis mid-papillary muscle two-dimensional echocardiogram was recorded from the parasternal approach. Subjects were then turned supine while peripheral intravenous, radial arterial, and pulmonary arterial catheters were inserted under local anesthesia. An infusion of 2–4 $mL \cdot kg^{-1} \cdot h^{-1}$ of lactated Ringer's solution was given throughout the rest of the study. Hemodynamic pressures were measured using Gould Statham transducers (model 23XL) and were continuously recorded (Gould digital model ES2000).

After completion of all preparations, each volunteer rested quietly until his hemodynamic variables varied less than 10% over 10 min. This usually required 30–60 min, after which baseline measurements were obtained of systemic and pulmonary arterial blood gases, standard hemodynamics including thermodilution cardiac outputs (using 10 mL of 0°C normal saline solution), and lead II of the electrocardiogram. For subject safety, pulmonary artery occlusion pressure was not obtained.

Anesthesia was induced by gradually increasing inspired concentrations of desflurane alone or desflurane and nitrous oxide in oxygen. Endotracheal intubation was performed after the end-tidal concentration of desflurane reached 12% and nitrous oxide was discontinued. No other drugs were administered. After the endotracheal tube was secured, a 5-MHz transesophageal echocardiographic probe (Hewlett Packard, Andover, Mass.) was positioned in the esophagus to image the same short-axis cross section recorded earlier from the parasternal view. Inspired gas concentrations and mechanical ventilation were then adjusted to obtain the appropriate levels of anesthesia and normocarbia. Normothermia was maintained by passive heating of the volunteer (Bair Hugger, Augustine Medical, Inc., Eden Prairie, Minn.). At each anesthetic level, after 12 min of stable end-tidal concentrations, the measurements taken at baseline were repeated and the transesophageal echocardiogram was recorded.

Hemodynamic measurements were obtained at end expiration. Customary formulas were used to calculate derived variables except that pulmonary artery diastolic pressure was substituted for pulmonary wedge pressure in the calculation of left ventricular stroke work index. Pulmonary vascular resistance was not calculated. The echocardiograms were analyzed for segmental wall-motion changes, as previously described (13). After orthogonal calibration, a video analysis system (Freeland CineView, Freeland Medical Systems, Louisville, Colo.) was used to measure end-diastolic and end-systolic cross-sectional cavity areas (EDA_c and ESA_c in cm^2) and circumferences (EDC_c and ESC_c in cm). In addition, total (i.e., cavity plus wall) left ventricular cross-sectional area at end systole (ESA_t in cm^2) was measured as the area enclosed by the left ventricular epicardium and the right ventricular side of the interventricular septum. All echocardiographic measurements were obtained for three cardiac cycles recorded at end expiration, and the mean of the three measurements was used. For 20 randomly selected intervals, the difference among the three measurements averaged 2.25 ± 1.75% (SD), with a maximum of 10.4%. For these same selected intervals, the measurements were repeated 2–8 wk later by the same observer without reference to the initial measurements. The difference between the means of the first and second measurements averaged 2.15 ± 1.78%, with a maximum of 7.5%. Area ejection fraction (EF_a in %) was calculated as

$$[(EDA_c - ESA_c)/EDA_c] \times 100.$$

Using a modification of the method of St. John Sutton, systolic wall stress (SWS in g/cm^2) was calculated as

$$(1.33 \times \text{SAP} \times \text{ESA}_c)/(\text{ESA}_t - \text{ESA}_c),$$

where SAP is systolic arterial pressure and 1.33 is a conversion factor (14). Left ventricular ejection time (ET in s) was determined by counting the number of video frames (produced by the echocardiograph at one every 33 ms) from end diastole to end systole. Ventricular end diastole was assumed to occur at the summit of the R wave of the simultaneously recorded electrocardiogram and end systole at the video frame where ESA_c was smallest. The heart rate-corrected velocity of circumferential fiber shortening (Vcfs_c) was calculated as

$$(\text{EDC}_c - \text{ESC}_c)/(\text{EDC}_c \times \text{ET}) \times \text{RR}^{1/2},$$

where RR is the duration of the cardiac cycle (15).

Data were analyzed using repeated-measures analysis of variance and *t*-tests. All values are expressed as the mean ± the standard deviation. A *P* value of 0.05 was used to test significance except where Bonferonni correction was required. To determine effects (if any) of the order of treatments, data obtained at comparable anesthetic levels but at different times were compared. For example, SAP at the 1.5 MAC level in the volunteers receiving nitrous oxide first was compared with SAP obtained in those receiving it last (about 2 h later).

Table 1. Demographics and Baseline Data

Variable	Mean	SD
Age (yr)	23.8	2.5
Weight (kg)	76.3	16.1
Height (cm)	181	7.8
BSA (m^2)	2.0	0.2
HR (beats/min)	69.8	6.2
SAP (mm Hg)	114	11.1
DAP (mm Hg)	67.6	9.1
MAP (mm Hg)	84.6	9.2
SPAP (mm Hg)	20.9	4.4
DPAP (mm Hg)	8.1	3.0
MPAP (mm Hg)	13.4	3.1
CVP (mm Hg)	5.0	2.7
CI (L·m^{-2})	3.7	0.4
SVR (dyne·s·cm^{-5})	901	154
LVSWI (g·m·m^{-2})	54.7	6.5
SVI (mL/m^2)	52.9	6.1
EDA_c (cm^2)	22.1	3.3
ESA_c (cm^2)	12.2	2.9
EF_a (%)	45.2	9.0
SWS (g/cm^2)	102	30.1
Vcfc (circ/s)	0.7	0.2
Pvo_2 (mm Hg)	48.0	3.2
BE_a (mEq/L)	1.9	2.4

BSA, body surface area; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; SPAP, systolic pulmonary arterial pressure; DPAP, diastolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure; CVP, central venous pressure; CI, cardiac index; SVR, systemic vascular resistance; LVSWI, left ventricular stroke work index; SVI, stroke volume index; EDA_c, left ventricular end-diastolic cross-sectional cavity area; ESA_c, left ventricular end-systolic cross-sectional cavity area; SWS, left ventricular systolic wall stress; EF_a, left ventricular area ejection fraction; Vcfc, heart rate-corrected velocity of circumferential fiber shortening; Pvo_2, mixed venous oxygen tension; BE_a, arterial base-excess.

Results

Eleven of our 12 volunteers completed the protocol without complication. One subject had evidence of pulmonary aspiration, first detected on the evening of the study, that resolved uneventfully with oral antibiotic therapy.

Hemodynamics, echocardiographic parameters, and blood-gas values obtained at baseline (awake) were within normal limits (Table 1). The effects of desflurane/nitrous oxide anesthesia were unaltered by the order of anesthetic administration (desflurane alone first or desflurane/nitrous oxide first).

Desflurane/nitrous oxide anesthesia decreased systemic blood pressures, cardiac index, systemic vascular resistance, and left ventricular stroke work index (Figure 1), and increased pulmonary arterial pressures and central venous pressure in a dose-dependent fashion (Figure 2), while heart rate was 10%–12% (Figure 2) and mixed venous oxygen tension was 2–4 mm Hg higher at all MAC levels than at baseline. Desflurane/nitrous oxide anesthesia modestly increased left ventricular end-diastolic cross-sectional area (preload) and decreased velocity of left ventricular circumferential fiber shortening, systolic wall stress (afterload), and area ejection fraction (Figure 3); this combination of changes indicated myocardial depression. The decrease in systolic wall stress was dramatic at the lowest (0.91) MAC level, but remained relatively constant thereafter. In contrast, the area ejection fraction increased slightly at 0.91 MAC, and then decreased significantly at higher concentrations of desflurane.

A complete report of the results obtained with desflurane alone are presented in an accompanying paper by Weiskopf et al. (16). However, at approximately comparable MAC levels, heart rate was lower and systemic blood pressures, central venous pressure, left ventricular stroke work index, and systemic vascular resistance usually were significantly higher during anesthesia with desflurane and nitrous oxide than during desflurane anesthesia alone (Table 2). After 7 h of desflurane anesthesia, regardless of the background gas, somewhat less cardiovascular depression and/or modest stimulation was apparent: cardiac index, area ejection fraction, velocity of left ventricular circumferential fiber shortening recovered

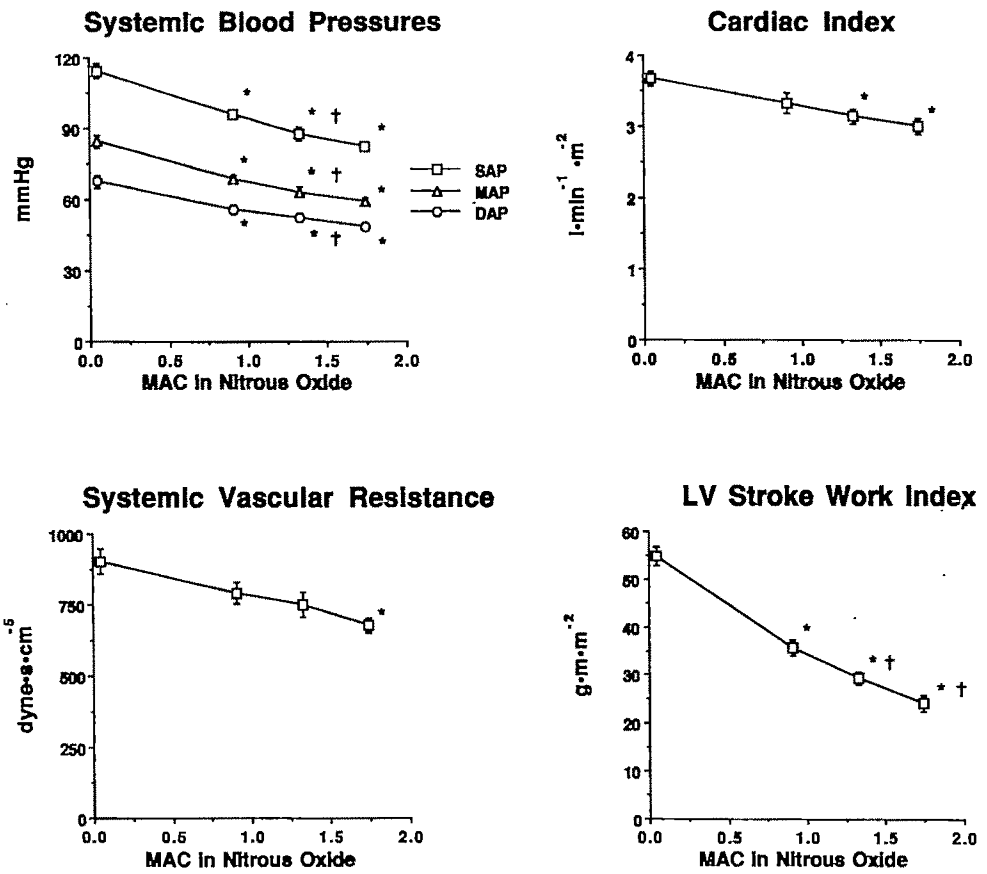

Figure 1. Systemic blood pressures (systolic, mean, and diastolic), cardiac index, systemic vascular resistance, left ventricular stroke work index with standard errors versus MAC of desflurane and nitrous oxide are shown. *Significant change when compared with the 0 MAC level (values obtained at baseline). †Significant change when compared with next lighter level of anesthesia.

to or toward awake values, whereas heart rate was further increased (Table 3). Evidence of circulatory insufficiency did not develop in any volunteer. Segmental left ventricular function was normal at baseline; and no segmental wall-motion abnormalities, ST-segment change, or dysrhythmias developed during study. Junctional rhythms were noted infrequently during induction of anesthesia and at other times, but never during measurement intervals. Premature ventricular contractions were not noted, except during manipulation of the pulmonary artery catheter.

Discussion

At normocarbia, 0.91–1.74 MAC of desflurane and nitrous oxide depressed the circulation in healthy young volunteers, but did not produce circulatory insufficiency. Despite a decrease in afterload (systolic wall stress) and maintenance of preload (end-diastolic cross-sectional area), ejection phase indices of contractility (area ejection fraction and velocity of left ventricular circumferential fiber shortening) decreased or were unchanged at the intermediate and highest desflurane concentrations, indicating that the combination of nitrous oxide and desflurane depressed myocardial contractility. A nonsignificant increase from baseline in the area ejection fraction and in the velocity of left ventricular circumferential fiber shortening (Figure 3) was noted at the lowest (0.91) MAC level probably because of the large, concomitant decrease in systolic wall stress. Supporting this hypothesis is our finding of an inverse correlation ($r = -0.68$) between these respective changes. However, at progressively higher concentrations of desflurane, these ejection phase indices of contractility decreased, whereas afterload remained constant and preload modestly increased. Despite this apparent myocardial depression, cardiac ejection remained near its baseline value, probably because systemic vasodilation produced by desflurane compensated for its direct depressant effects. Moreover, prolonged anesthesia with desflurane plus nitrous oxide did not show worsening depression, but in fact, some recovery of left ventricular function was apparent. Although the extent of this recovery of

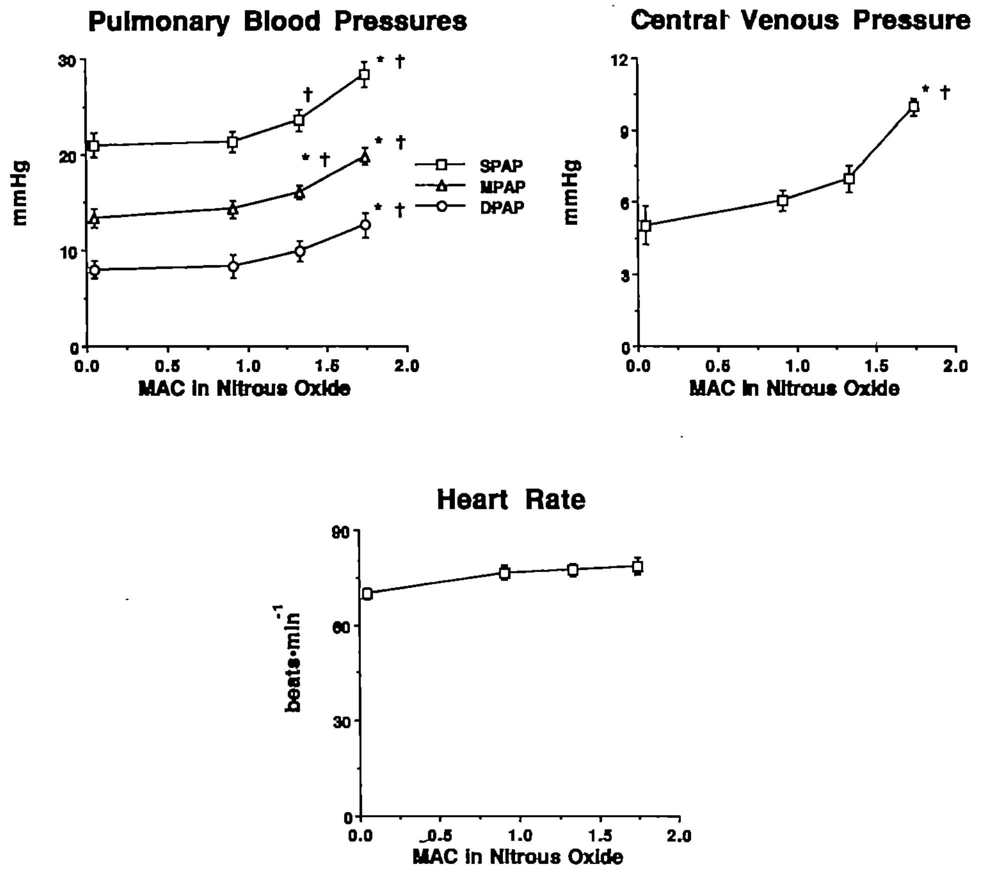

Figure 2. Heart rate, pulmonary blood pressures (systolic, mean, and diastolic), and central venous pressure with standard errors versus MAC of desflurane and nitrous oxide are shown. *Significant change when compared with the 0 MAC level (values obtained at baseline). †Significant change when compared with next lighter level of anesthesia. Repeated-measures analysis of variance indicates significant change in heart rate ($P < 0.007$), but *t*-tests between means do not reach significance ($P < 0.01$).

function was modest and its etiology uncertain, its consistent occurrence argues strongly against any cumulative effect of desflurane on myocardial performance.

Because desflurane and nitrous oxide increased pulmonary arterial blood pressures, right, rather than left, ventricular depression was more apparent (central venous pressure increased from 5 mm Hg at baseline to 10 mm Hg at 1.74 MAC). Nitrous oxide is not likely to have been the primary cause for this pulmonary effect, as pulmonary hemodynamics comparably increased during desflurane alone and previous studies have shown that nitrous oxide has little effect on pulmonary vascular resistance (17–19). However, the presence of nitrous oxide may account partially for the increase in central venous pressure, because its sympathomimetic effects may increase peripheral venous tone and, thereby, venous return to the right ventricle (20).

At 1.74 (highest) MAC anesthesia, the combination of nitrous oxide and desflurane depressed systemic blood pressures less, and (perhaps thereby) increased heart rate less, than 1.66 MAC of desflurane alone. The smaller decrease in systemic blood pressures in the presence of nitrous oxide was due to better maintenance of systemic vascular resistance, not cardiac output (Table 2). However, in this healthy group of volunteers at "lighter" levels of anesthesia or after prolonged anesthesia, the hemodynamic differences consequent to combining nitrous oxide and desflurane appear minimal.

In most respects, desflurane/nitrous oxide anesthesia produces hemodynamic changes similar to those produced by isoflurane/nitrous oxide anesthesia. In a similar experiment in unstimulated volunteers anesthetized to comparable levels with isoflurane and 70% nitrous oxide, Dolan et al. (21) found a dose-dependent depression of systemic blood pressures (13%–27% in mean arterial blood pressure) and systemic vascular resistance (3%–35%), and modest increases in heart rate (10%–33%) and central venous pressure (0–2.3 mm Hg). In contrast to our findings, cardiac output was preserved at all levels of isoflurane/nitrous oxide anesthesia. For comparison, we

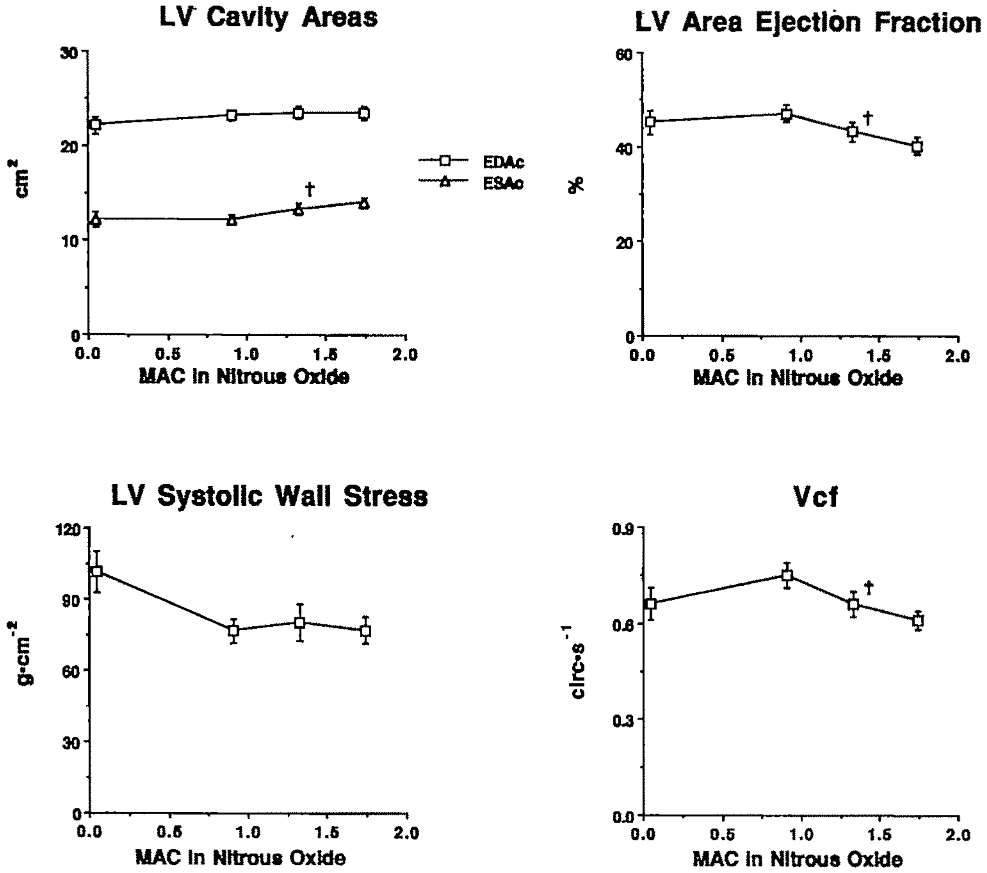

Figure 3. Left ventricular cavity areas (end-diastolic, *upper trace*; end-systolic cross-sectional areas, *lower trace*), left ventricular systolic wall stress, left ventricular area ejection fraction, and heart rate-corrected velocity of circumferential fiber shortening with standard errors versus MAC of desflurane and nitrous oxide are shown. †Significant change when compared with next lighter level of anesthesia. Repeated-measures analysis of variance indicates significant change in all shown variables ($P < 0.05$), but most t-tests between means do not reach significance ($P < 0.01$).

Table 2. Differences Noted Between Desflurane/N$_2$O and Desflurane/O$_2$[a]

Variable	Level	N$_2$O value is	By
BE	1.74 vs 1.66	Lower	1.0 mEq/L
HR	1.74 vs 1.66	Lower	13 beats/min
SAP	0.91 vs 0.83	Higher	10 mm Hg
SAP	1.74 vs 1.66	Higher	14 mm Hg
MAP	0.91 vs 0.83	Higher	8 mm Hg
DAP	0.91 vs 0.83	Higher	6 mm Hg
DAP	1.74 vs 1.66	Higher	7 mm Hg
CVP	1.74 vs 1.66	Higher	1.5 mm Hg
LVSWI	0.91 vs 0.83	Higher	5.6 g·m·m^{-2}
SVR	1.74 vs 1.66	Higher	176 dyne·s·cm^{-5}

[a] Compared with the data of Weiskopf et al. (16) at comparable anesthetic levels (0.83, 1.24, and 1.66 MAC). "Level" is the MAC multiple. We have assumed that 60% nitrous oxide when present contributes 0.5 MAC. See Table 1 for definition of abbreviations.

Table 3. Differences Noted With Prolonged Desflurane/N$_2$O[a]

Variable	Level	Late value is	By
HR	0.91 and 1.74	Higher	10–14 beats/min
CI	0.91 and 1.74	Higher	0.9 L/m^2
SVI	1.74	Higher	6 mL/m^2
LVSWI	1.74	Higher	6 g·m·m^{-2}
EF$_a$	0.91 and 1.74	Higher	6–8%
VCF	1.74	Higher	0.1 circ/s
SVR	1.74	Lower	92 dyne·s·cm^{-5}

[a] Based on paired t-test and $P < 0.05$. "Level" is the MAC multiple. We have assumed that 60% nitrous oxide contributes 0.5 MAC. "Late value" is the mean value of the variable listed obtained after the seventh hour of anesthesia with desflurane compared to the value obtained for the same variable at an identical end-tidal concentration of desflurance and nitrous oxide during the first 90 min of anesthesia. See Table 1 for definition of abbreviations.

have plotted our data for heart rate, mean arterial pressure, cardiac index, central venous pressure, systemic vascular resistance, and stroke volume index together with data from Dolan et al. (21) and Bahlman et al. (22) who studied the effects of halothane and nitrous oxide in unstimulated volunteers (Figure 4).

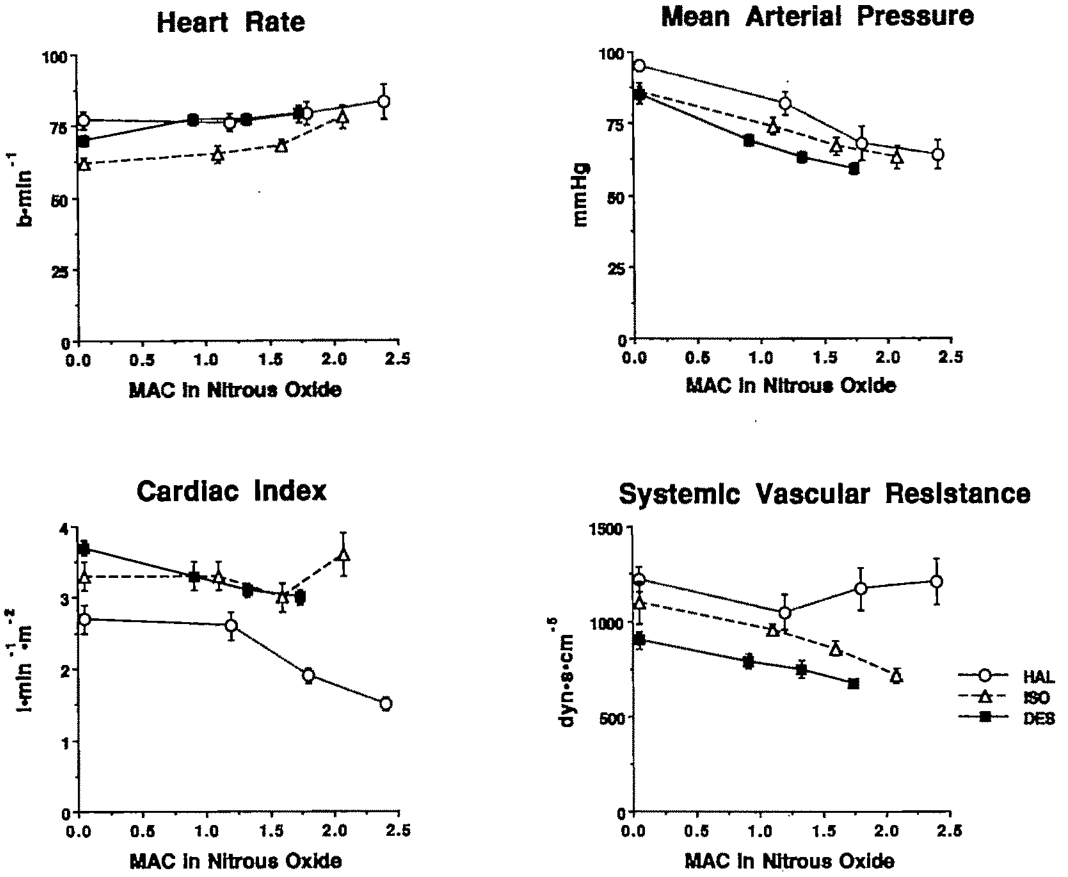

Figure 4. Heart rate, mean arterial pressure, cardiac index, and systemic vascular resistance with standard errors versus MAC are shown for patients in this study who received desflurane and 60% nitrous oxide (DES), for patients of Dolan et al. (21) who received isoflurane and 70% nitrous oxide (ISO), and those of Bahlman et al. (22) who received halothane and 70% nitrous oxide (HAL).

The authors gratefully acknowledge the assistance of Winifred von Ehrenburg and Celeste Mangold in editing and preparing this manuscript.

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Cardiovascular Actions of Desflurane With and Without Nitrous Oxide During Spontaneous Ventilation in Humans

Richard B. Weiskopf, MD, Michael K. Cahalan, MD, Pompiliu Ionescu, MD,
Edmond I. Eger II, MD, Nobuhiko Yasuda, MD, Stephen H. Lockhart, PhD, MD,
Ira J. Rampil, MD, Michael Laster, DVM, Beth Freire, BS, and Natalie Peterson, BS

Departments of Anesthesia and Physiology and the Cardiovascular Research Institute, University of California,
San Francisco, California

We investigated the cardiovascular actions of desflurane (formerly I-653) during spontaneous ventilation. We gave 0.8–0.9, 1.2–1.3, and 1.6–1.7 MAC desflurane in oxygen ($n = 6$) and in 60% nitrous oxide, balance oxygen ($n = 6$) to unmedicated healthy male volunteers. Both anesthetic regimens decreased ventilation, increased partial pressure of arterial carbon dioxide, and produced similar cardiovascular changes. In comparison with values obtained when the volunteers were conscious, desflurane anesthesia with spontaneous ventilation decreased systemic vascular resistance and mean arterial blood pressure. Cardiac index, heart rate, stroke volume index, and central venous blood pressure increased. Left ventricular ejection fraction increased at 0.83 MAC desflurane in oxygen, and otherwise did not differ from the conscious value. The velocity of ventricular circumferential fiber shortening, estimated by echocardiography, increased with desflurane in oxygen but did not change with desflurane in nitrous oxide. Oxygen consumption increased during desflurane and oxygen anesthesia, but not when nitrous oxide plus oxygen was the background gas. Desflurane increased oxygen transport, the ratio of oxygen transport to oxygen consumption, mixed venous partial pressure of oxygen, and oxyhemoglobin saturation. The cardiovascular changes with desflurane during spontaneous ventilation differ from those during controlled ventilation. With both background gases, spontaneous ventilation, in comparison with controlled ventilation, increased cardiac index, stroke volume, central venous pressure, left ventricular ejection fraction, velocity of circumferential fiber shortening, oxygen transport, and the ratio of oxygen transport to oxygen consumption but did not change mean arterial blood pressure except at 1.66 MAC desflurane in oxygen (when it was higher with spontaneous than with controlled ventilation).

(Anesth Analg 1991;73:165–74)

Desflurane, formerly known as I-653, is a new inhalation anesthetic with several advantages over other inhaled anesthetics. Its low blood (1) and tissue (2) solubilities result in rapid washin and washout (3) and rapid emergence from anesthesia (4). It is stable in vitro (5) and undergoes little or no metabolism in rats (6), swine (7), and humans (8), thus limiting its potential for toxicity (9). However, in swine maintained normocapnic by mechanical ventilation of their lungs, desflurane causes cardiovascular depression equivalent to that of isoflurane (10). As described in accompanying papers (11,12), desflurane produces little cardiovascular change at 0.83 MAC in ventilated normocapnic humans, but causes cardiovascular depression at greater anesthetic concentrations.

Desflurane depresses ventilation and increases partial pressure of arterial carbon dioxide (Pa_{CO_2}) in swine (13) and humans (14). Because changes in intrathoracic pressure and Pa_{CO_2} alter cardiovascular variables and the changes in them induced by anesthetics, we determined the cardiovascular actions of desflurane with or without nitrous oxide during spontaneous ventilation in healthy male volunteers.

Methods

These studies were performed with the approval of the Committee on Human Research of the University of California, San Francisco, and with informed consent of the same 12 healthy male volunteers who participated in studies described in the accompany-

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Supported by the Anesthesia Research Foundation and a grant from Anaquest, Inc.

Accepted for publication April 4, 1991.

Address correspondence to Dr. Weiskopf, Department of Anesthesia, University of California, San Francisco, CA 94143-0648.

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0003-2999/91/$3.50

ing manuscripts (11,12). The measurement of cardiovascular variables are described in accompanying papers (11,12). Volunteers were studied while conscious and while anesthetized with desflurane at three steady-state end-tidal concentrations (0.83, 1.24, and 1.66 MAC, assuming 60% nitrous oxide is equivalent to 0.5 MAC). The two lower concentrations were administered in random order; but for safety, the highest concentration always was given last. The order of administration of background gas (oxygen alone or 60% nitrous oxide in oxygen) was randomized. All volunteers received all concentrations of desflurane with both background gases, with ventilation controlled to maintain normal Paco$_2$. After cardiovascular measurements were completed, subjects breathed spontaneously and received the same three randomized concentrations of desflurane in the second background gas they received. To limit the duration of anesthesia to 7 h for each volunteer, studies with spontaneous ventilation were performed with only one background gas per volunteer. Thus, six subjects spontaneously breathed desflurane in oxygen, and the other six spontaneously breathed desflurane in 60% nitrous oxide plus oxygen.

We performed the same cardiovascular measurements and calculations in the conscious and the anesthetized volunteers: mean systemic and pulmonary arterial blood pressures, central venous pressures, cardiac index, heart rate, calf (muscle) blood flow, arterial and mixed venous partial pressures of oxygen (Po$_2$) and carbon dioxide (Pco$_2$), pH, and oxyhemoglobin saturation, stroke volume index, systemic vascular resistance, oxygen consumption, oxygen transport, ratio of oxygen transport to oxygen consumption, base-excess, left ventricular end-diastolic and end-systolic cross-sectional cavity areas and circumferences, systolic wall stress, and velocity of circumferential fiber shortening corrected for heart rate (11,12). However, because thermodilution measurement of cardiac output requires approximately 20 s, this measurement could not be limited to the period of end-expiration (the time of injection) as it was in the studies with controlled ventilation.

Table 1. Conscious Values

Variable	O_2 group	N_2O group
Age (yr)	23.5 ± 1.2	24.2 ± 0.9
Height (cm)	179.5 ± 2.0	182.3 ± 4.2
Weight (kg)	76.8 ± 6.4	75.8 ± 7.4
BSA (m^2)	1.95 ± 0.08	1.96 ± 0.11
Temperature (°C)	36.72 ± 0.13	36.70 ± 0.09
HR (beats/min)	71 ± 3	69 ± 2
MAP (mm Hg)	88 ± 4	81 ± 3
MPAP (mm Hg)	13.5 ± 1.3	13.3 ± 1.4
CVP (mm Hg)	5.4 ± 1.3	4.7 ± 1.0
CI ($L \cdot min \cdot m^{-2}$)	3.69 ± 0.18	3.65 ± 0.14
SVR ($dyne \cdot s \cdot cm^{-5}$)	935 ± 84	868 ± 35
SVI (mL/m^2)	52.4 ± 2.9	53.4 ± 2.3
LVEDA (cm^2)	21.6 ± 1.1	22.5 ± 1.6
LVESA (cm^2)	12.1 ± 1.2	12.2 ± 1.2
LVEF (%)	44 ± 4	46 ± 4
SWS (g/cm^2)	98 ± 16	106 ± 9
Vcfs (circ/s)	0.65 ± 0.07	0.67 ± 0.06
Pao$_2$ (mm Hg)	102 ± 4	102 ± 3
Paco$_2$ (mm Hg)	40.3 ± 1.1	42.5 ± 0.7
pHa (U)	7.436 ± 0.021	7.401 ± 0.004
Pvo$_2$ (mm Hg)	47.3 ± 1.3	48.6 ± 1.4
Svo$_2$ (%)	82.6 ± 1.2	82.6 ± 1.1
To$_2$ (mL $O_2 \cdot min^{-1} \cdot m^{-2}$)	17.9 ± 1.0	17.7 ± 0.6
Vo$_2$ (mL $O_2 \cdot min^{-1} \cdot m^{-2}$)	2.75 ± 0.18	2.69 ± 0.14
To$_2$/Vo$_2$	6.64 ± 0.66	6.65 ± 0.62
Base-excess (mEq/L)	2.7 ± 1.4	1.1 ± 0.3

O_2 group, received desflurane anesthesia in ogygen; N_2O group, received desflurane in 60% nitrous oxide plus oxygen; BSA, body surface area; HR, heart rate; MAP, mean arterial blood pressure; MPAP, mean pulmonary arterial blood pressure; CVP, central venous pressure; CI, cardiac index; SVR, systemic vascular resistance; SVI, stroke volume index; LVEDA, left ventricular end-diastolic cross-sectional cavity area; LVESA, left ventricular systolic cross-sectional cavity area; LVEF, left ventricular ejection fraction; Vcfs, velocity of circumferential fiber shortening; SWS, systemic wall stress; Pao$_2$, arterial oxygen tension; Paco$_2$, arterial carbon dioxide tension; Pvo$_2$, mixed venous blood partial pressure of oxygen; Svo$_2$, mixed venous oxyhemoglobin saturation; To$_2$/Vo$_2$, ratio of oxygen transport to oxygen consumption.

Data are mean ± SE, n = 6 per group.

For each variable, we tested the cardiovascular actions of desflurane during spontaneous ventilation (separately in oxygen or in nitrous oxide plus oxygen) using analysis of variance with repeated measures and Newman-Keuls method of multiple comparisons (15). We tested by paired *t*-test for differences between desflurane in oxygen and desflurane in nitrous oxide plus oxygen in each variable at each anesthetic concentration. To conserve the number of volunteers exposed to an experimental anesthetic, these volunteers were the same as those in whom we evaluated the cardiovascular response to desflurane with controlled ventilation. Thus, using paired *t*-tests we tested for differences (if any) in each variable between controlled and spontaneous ventilation, separately at each concentration of desflurane. In all instances, statistical significance was accepted at $P \leq 0.05$.

Results

The two groups of subjects did not differ in physical characteristics or in measured or calculated cardiovascular variables while they were conscious (Table 1).

As described in an accompanying paper (14), all concentrations of desflurane studied depressed ventilation and thus increased Paco$_2$ and decreased arterial pH (Figure 1). The cardiovascular effects of desflurane anestheisa with spontaneous ventilation were generally similar with the two background gases. Desflurane decreased systemic vascular resistance and mean arterial blood pressure from values

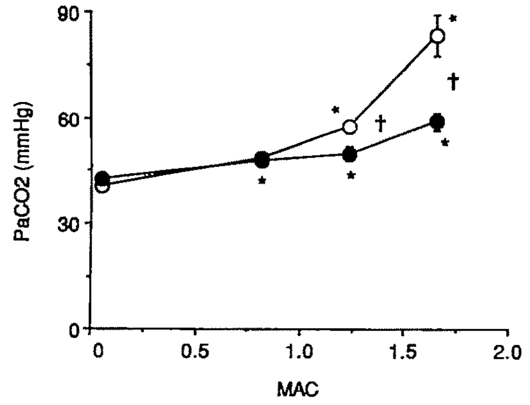

Figure 1. Effect of desflurane in oxygen (○) or in 60% N_2O (●) on resting Pa_{CO_2}. Data are mean ±SE. $n = 6$ per group. $^*P \leq 0.05$ vs conscious. $†P \leq 0.05$, O_2 vs N_2O.

obtained while volunteers were conscious (Figure 2). Cardiac index, heart rate, central venous blood pressure, and muscle blood flow increased in the presence of both background gases, whereas stroke volume index increased with desflurane in oxygen but not with desflurane in nitrous oxide (Figures 2 and 3). The echocardiographic measure of preload (left ventricular end-diastolic cross-sectional area) did not change from the conscious value with any desflurane concentration in either background gas (Figure 2), whereas the measure of afterload (systolic wall stress) decreased at all desflurane concentrations in both background gases (Figure 2). The velocity of left ventricular fiber shortening increased at all desflurane concentrations in oxygen (Figure 2) but was unchanged at any desflurane concentration in nitrous oxide (Figure 2), whereas left ventricular ejection fraction increased only at 0.83 MAC desflurane in oxygen (Figure 3). Oxygen consumption increased during desflurane without but not with nitrous oxide (Figure 4). The values of oxygen transport, ratio of oxygen transport to oxygen consumption, mixed venous P_{O_2}, and oxyhemoglobin saturation were higher at all desflurane concentrations than when the volunteers were conscious (Figure 4).

During spontaneous ventilation at 1.66 MAC, ventilation was less depressed, and thus, Pa_{CO_2} was lower and pHa was higher in the presence of nitrous oxide than in that of oxygen (Figure 1). At lower anesthetic concentrations, background gas did not change ventilatory variables. Partial pressures of oxygen in arterial and mixed venous blood were higher when the subjects breathed desflurane in oxygen than when 60% nitrous oxide was substituted for oxygen. The only cardiovascular difference associated with the substitution of 60% nitrous oxide for 0.5 MAC desflurane was a higher mean systemic arterial blood pressure at 0.83 and 1.24 MAC (Figure 3). At 1.66 MAC, substitution of nitrous oxide did not alter blood pressure nor any other cardiovascular variable.

The cardiovascular changes seen with desflurane during spontaneous ventilation differ from those during controlled ventilation. With both background gases, cardiac index, stroke volume index, central venous blood pressure, left ventricular ejection fraction, velocity of circumferential fiber shortening, oxygen consumption, oxygen transport, ratio of oxygen transport to oxygen consumption, mixed venous P_{O_2}, and oxyhemoglobin saturation were greater with spontaneous ventilation than with controlled ventilation (Figures 5 and 6). Mean arterial blood pressure did not differ between controlled and spontaneous ventilation except at 1.66 MAC desflurane in oxygen. Muscle blood flow was greater with spontaneous ventilation than with controlled ventilation at 0.83 MAC with both background gases, at 1.24 MAC with desflurane in nitrous oxide but not in oxygen, and did not differ between spontaneous and controlled ventilation at 1.66 MAC with either background gas. The echocardiographic measures of preload and afterload, left ventricular end-diastolic cross-sectional area and systolic wall stress, respectively, did not differ between controlled and spontaneous ventilation at any desflurane concentration in either background gas.

Discussion

All modern halogenated inhalation anesthetics depress cardiovascular function, myocardial contractility, and ventilation. Anesthetics attenuate but do not obliterate the cardiovascular stimulation caused by increased Pa_{CO_2} (16–20). As we did not conduct a steady-state dose-response study examining cardiovascular changes during hypercapnia while volunteers were conscious and while they were anesthetized, we cannot quantify precisely the extent to which desflurane alters the cardiovascular response to carbon dioxide. The differences in Pa_{CO_2} at different anesthetic levels further confound this effect; that is, a greater attenuation of the cardiovascular response at deeper anesthetic levels might be offset by a greater increase in Pa_{CO_2}. However, we measured mean arterial blood pressure and heart rate while the volunteers performed the Read rebreathing tests (14). The increase in heart rate per increase in Pa_{CO_2} at 1.66 MAC desflurane did not differ from that when the volunteers were conscious. This might indicate that desflurane causes less blunting of the cardiovascular response to carbon dioxide than do other halogenated inhaled anesthetics, or, that at higher anesthetic concentrations, desflurane caused some direct, or more likely, indirect stimulation,

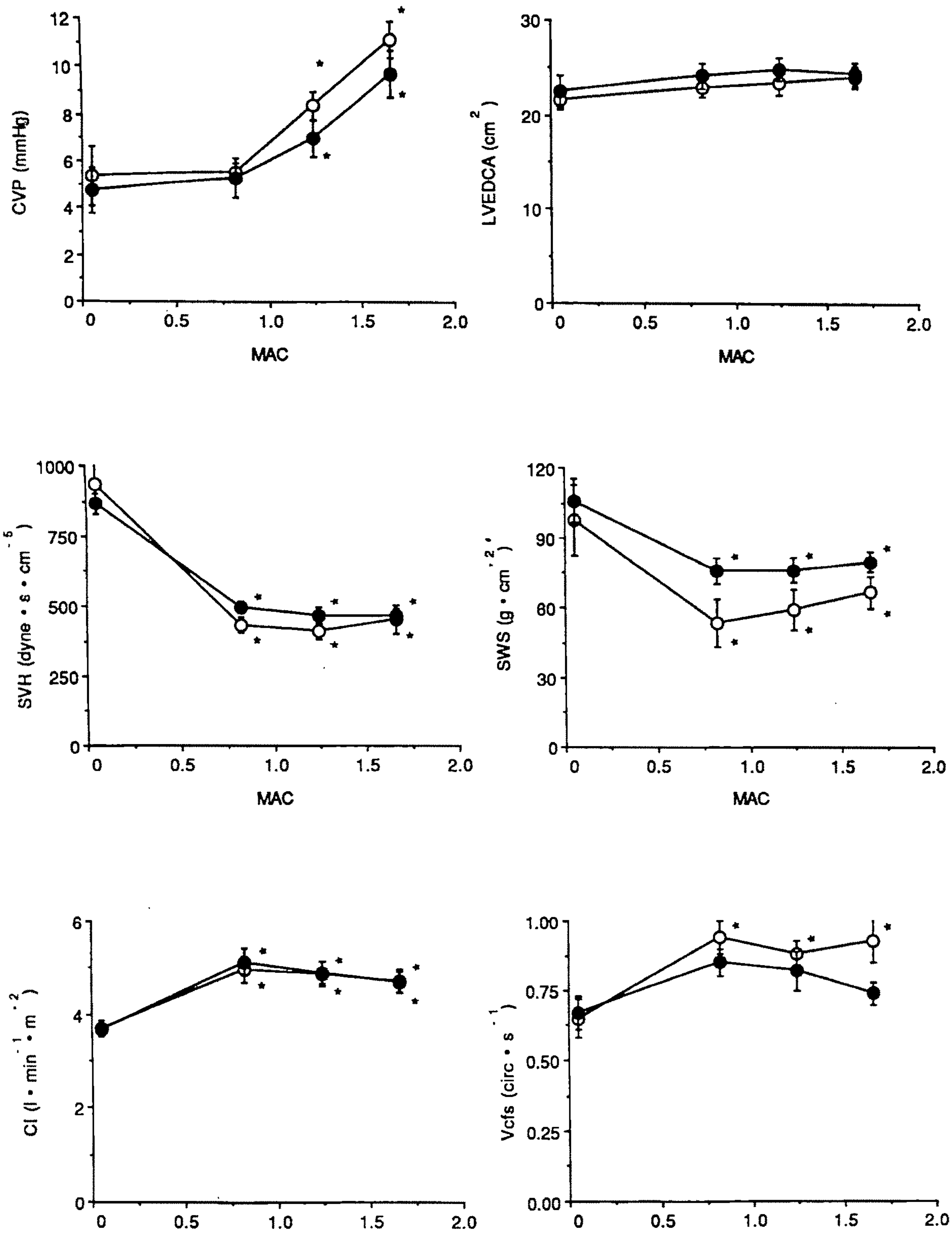

Figure 2. Central venous blood pressure (CVP), systemic vascular resistance (SVR), cardiac index (CI), left ventricular end-diastolic cross-sectional area (LVEDCA), left ventricular systolic wall stress (SWS), and velocity of left ventricular circumferential fiber shortening (Vcfs) during spontaneous ventilation in humans when conscious (0 MAC) and during desflurane anesthesia in oxygen (○) or 60% N_2O (●). $^*P \leq 0.05$ vs conscious.

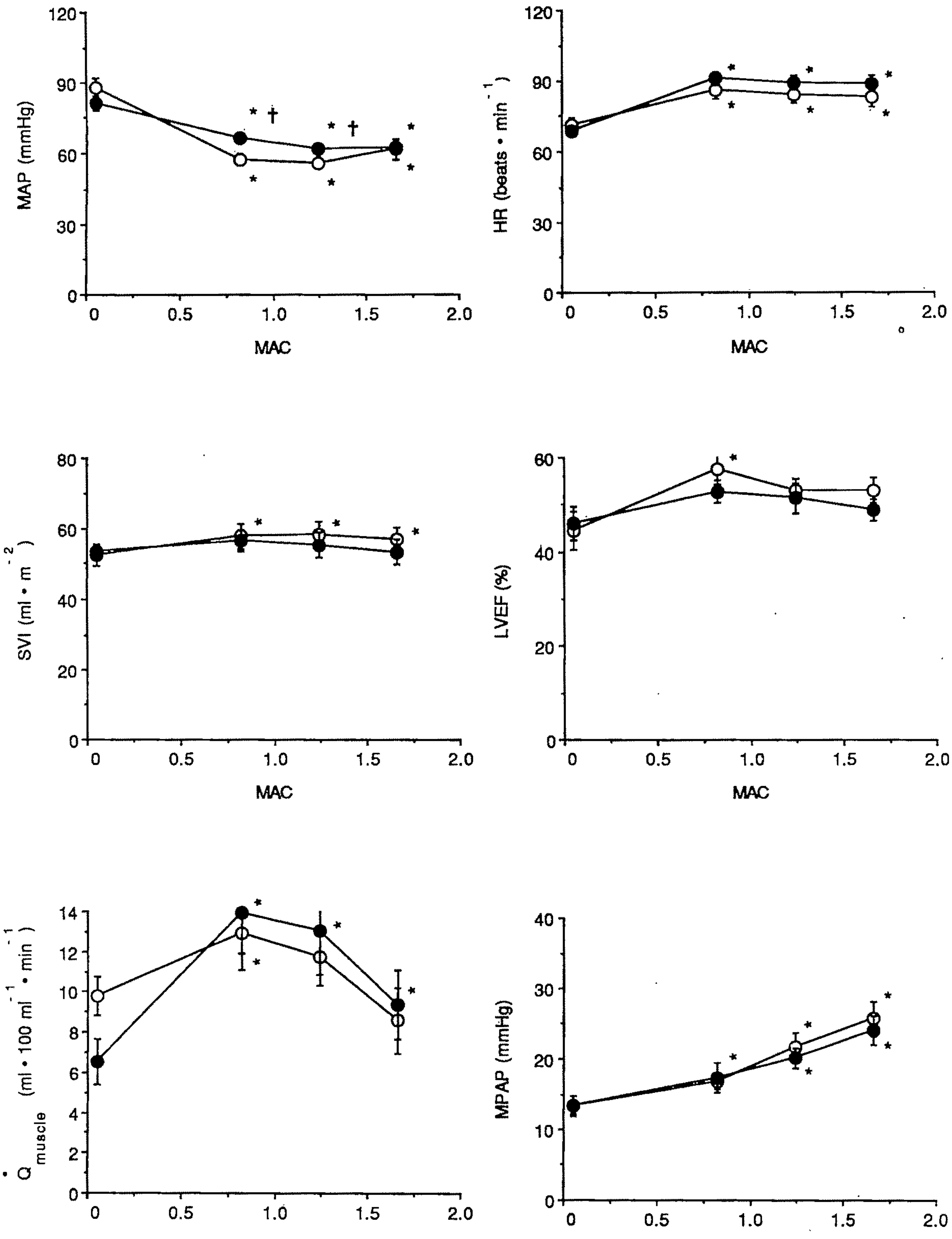

Figure 3. Mean arterial blood pressure (MAP), stroke volume index (SVI), muscle blood flow ($\dot{Q}_{muscle}$), heart rate (HR), left ventricular ejection fraction (LVEF), and mean pulmonary arterial blood pressure (MPAP) during spontaneous ventilation in humans when conscious (0 MAC) and during desflurane anesthesia in oxygen (○) or 60% N_2O (●). *$P \leq 0.05$ vs conscious. †$P \leq 0.05$, O_2 vs N_2O.

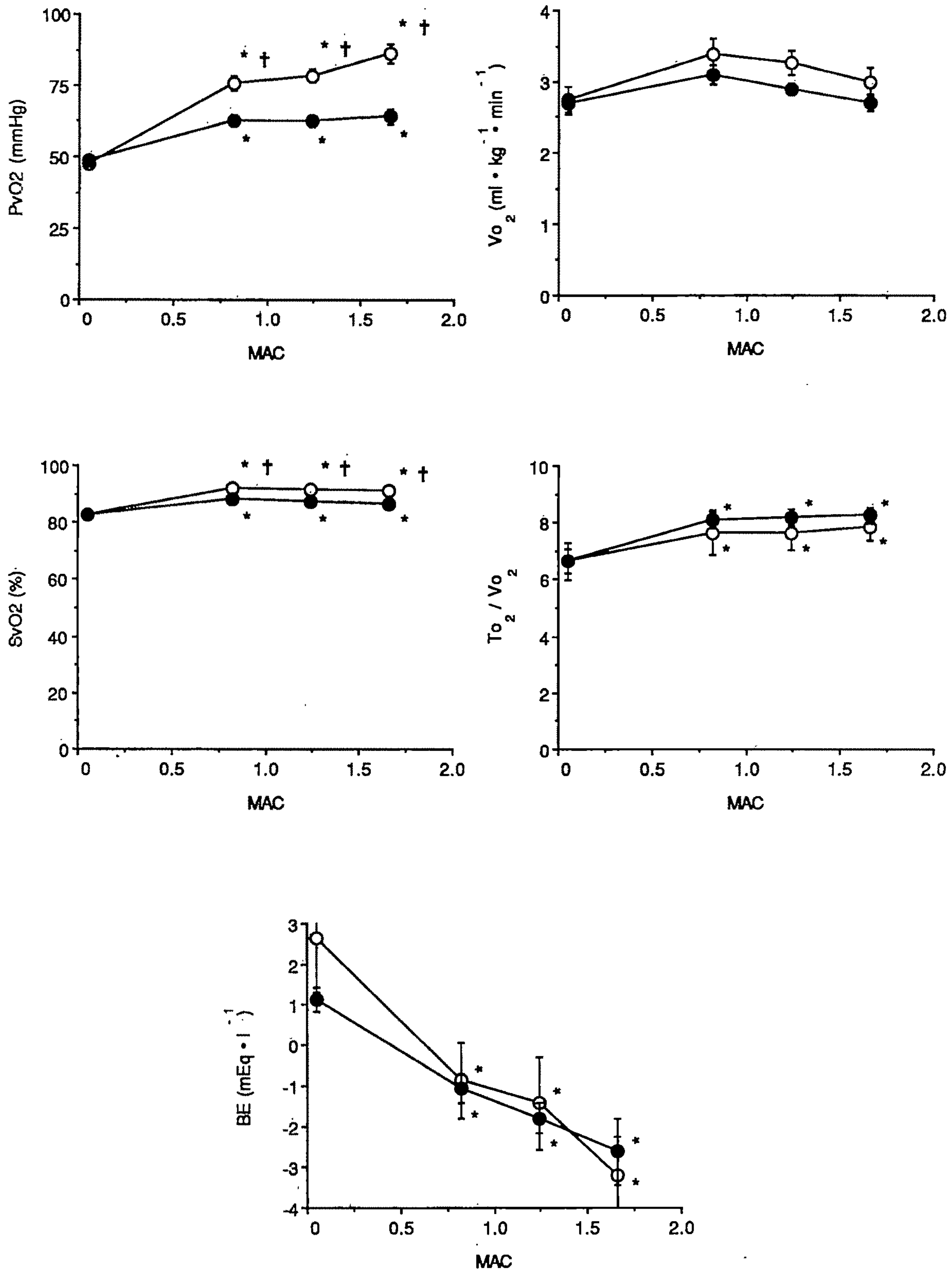

Figure 4. Mixed venous Po_2 (Pvo_2), mixed venous oxyhemoglobin saturation (Svo_2), oxygen consumption (Vo_2), ratio of oxygen transport to consumption (To_2/Vo_2), and arterial blood base-excess (BE) during spontaneous ventilation in humans when conscious (0 MAC) and during desflurane anesthesia in oxygen (○) or 60% N_2O (●). $*P \leq 0.05$ vs conscious. $†P \leq 0.05$, O_2 vs N_2O.

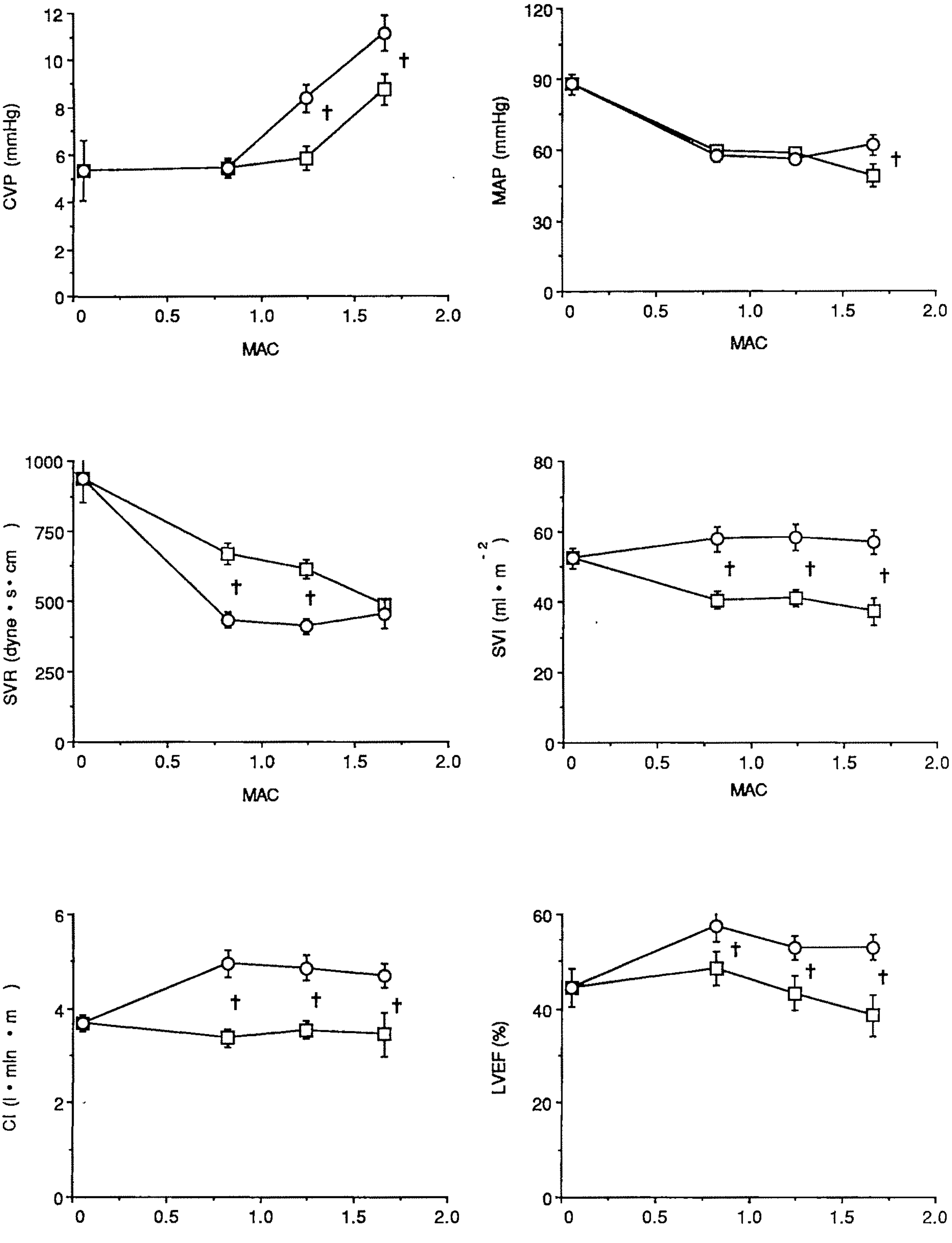

Figure 5. Central venous blood pressure (CVP), systemic vascular resistance (SVR), cardiac index (CI), mean arterial blood pressure (MAP), stroke volume index (SVI), and left ventricular ejection fraction (LVEF) during desflurane anesthesia in oxygen with spontaneous (○) and controlled (□) ventilation in humans. †$P \leq 0.05$, spontaneous vs controlled ventilation.

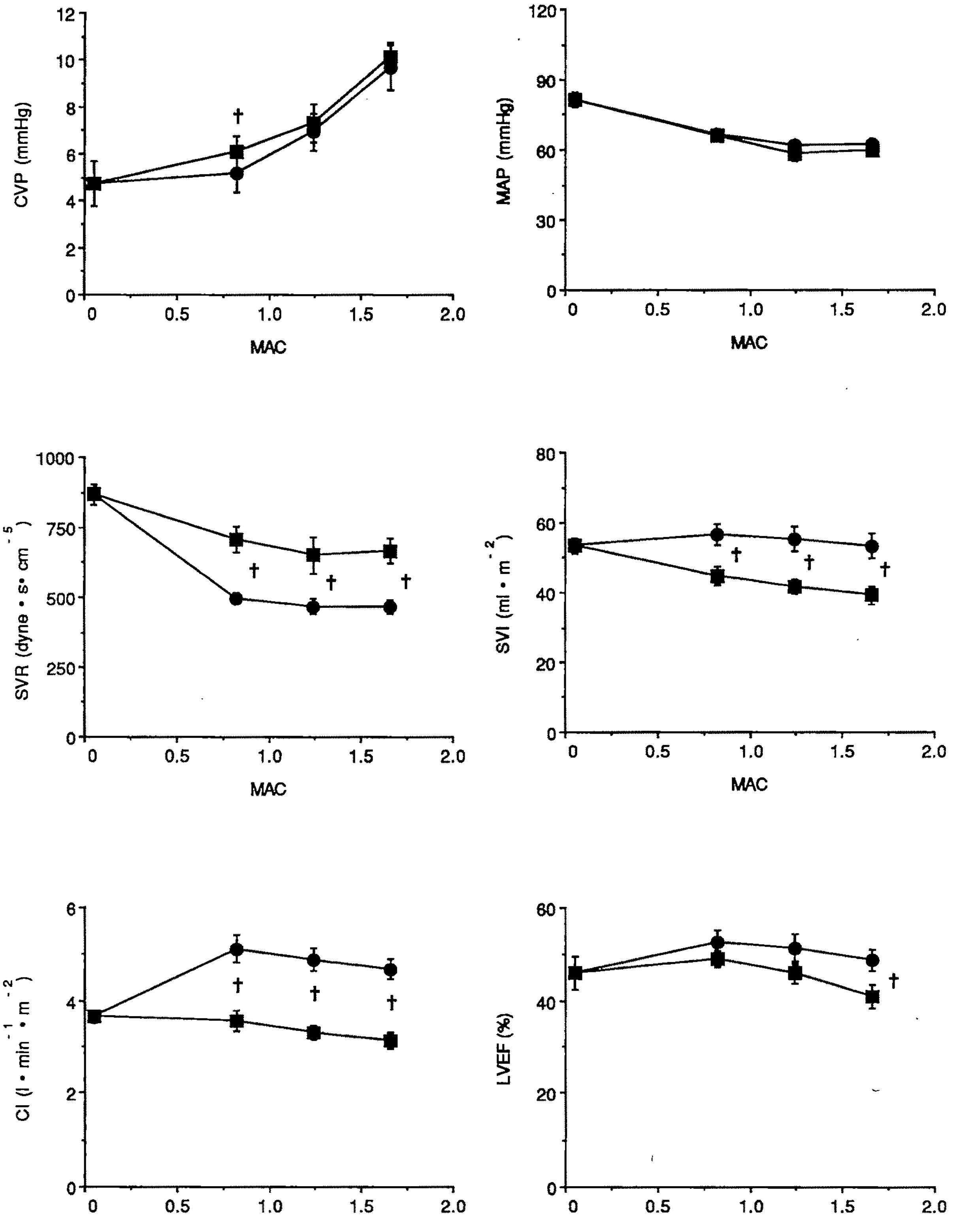

Figure 6. Central venous blood pressure (CVP), systemic vascular resistance (SVR), cardiac index (CI), mean arterial blood pressure (MAP), stroke volume index (SVI), and left ventricular ejection fraction (LVEF) during desflurane anesthesia in 60% N_2O with spontaneous (●) and controlled (■) ventilation in humans. †$P \leq 0.05$, spontaneous vs controlled ventilation.

which overrides the direct depression. Our data do not permit us to distinguish between these possible effects.

Nevertheless, the cardiovascular actions of desflurane observed during spontaneous ventilation are likely a combination of direct desflurane-induced depression and indirect hypercarbic-induced stimulation. The decreases in systemic vascular resistance and mean arterial blood pressure are similar to those observed in normocapnic swine (10) and in humans (11), and therefore are likely attributable to the direct actions of desflurane. Similarly, the echocardiographic estimate of afterload (systolic wall stress) decreased. Our estimates of preload were inconsistent: central venous pressure increased whereas left ventricular end-diastolic cross-sectional area did not change. We cannot determine if the increases in cardiac output and in left ventricular fiber shortening reflect a net increase in myocardial contractility or are the result of decreased afterload and either unchanged or increased preload.

The increase in heart rate and cardiac output and decrease in systemic vascular resistance during desflurane anesthesia with spontaneous ventilation are qualitatively similar to the actions of halothane (20,21), enflurane (22), and isoflurane (19), except for the lack of change in cardiac output with halothane (20,21).

Increased venous return to the right-side of the heart (as evidenced by increased central venous pressure, Figures 5 and 6) associated with negative intrathoracic pressure caused by spontaneous ventilation and by the avoidance of increased intrathoracic pressure (23) also likely contributed to the cardiovascular differences observed during spontaneous ventilation compared with controlled ventilation. This study was not designed to assess the relative contributions of these factors. However, hypercapnia appears to provide the greater effect, because the cardiovascular stimulation persisted with 1.66 MAC desflurane in oxygen when tidal volume (and therefore, likely, negative intrathoracic pressure) was greatly reduced. In addition, the higher concentration of desflurane may have blunted the stimulation produced by increased $Paco_2$ as noted earlier.

During controlled ventilation at comparable anesthetic depth, substitution of nitrous oxide for an equipotent amount of desflurane decreased heart rate and increased mean arterial blood pressure, central venous pressure, and systemic vascular resistance. These differences disappeared with spontaneous ventilation. It is possible that the differences in cardiovascular function during controlled ventilation were caused by nitrous oxide-induced mild sympathetic stimulation (20). Compared with the hypercapneic-induced sympathetic stimulation, this stimulation may have been sufficiently small that the effect of the hypercapnia thus overrode and obscured the effect of nitrous oxide.

The cardiovascular differences between spontaneous and controlled ventilation during desflurane anesthesia are similar generally to those observed by Cromwell et al. (19) with isoflurane anesthesia, except at the deepest anesthetic level: with desflurane, lesser heart rate and greater mean arterial blood pressure were observed with spontaneous ventilation, whereas with isoflurane, no differences in these variables were noted. In addition, the decreased systemic vascular resistance noted during spontaneous ventilation at all concentrations of isoflurane anesthesia was not observed at the highest desflurane concentration. It is possible that the relatively lesser decrease in systemic vascular resistance in our subjects resulted in the relatively lesser decrease in blood pressure, thereby providing less baroreceptor-mediated effect on heart rate. These differences could result from differences in experimental design or from our subjects having been given a higher anesthetic concentration of desflurane (1.66 MAC) than the concentration of isoflurane (1.41 MAC) given to Cromwell's subjects. Alternatively, the relatively smaller decrease in systemic vascular resistance seen with desflurane could be the result of greater circulating concentrations or activity of one or more vasoactive substances. However, in normocapnic swine anesthetized with desflurane or isoflurane, although dose-dependent increases in plasma renin activity and vasopressin but not catecholamine concentrations are found, they do not differ as a function of the anesthetics (24).

Spontaneous ventilation improves the safety of inhaled anesthetic administration because the concentration producing cardiovascular collapse is greater than that producing apnea (13). The diminished cardiovascular depression associated with desflurane anesthesia administered by spontaneous ventilation in humans adds to that safety. Stroke volume does not change, cardiac index is increased in comparison with the conscious state, and the decrease in blood pressure is less than that seen with controlled ventilation. This diminished cardiovascular depression during spontaneous ventilation is reflected in increases in variables suggested as markers of adequacy of oxygen transport and tissue oxygenation (13): ratio of oxygen transport to oxygen consumption, mixed venous Po_2, and oxyhemoglobin saturation.

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Does Desflurane Modify Circulatory Responses to Stimulation in Humans?

Nobuhiko Yasuda, MD, Richard B. Weiskopf, MD, Michael K. Cahalan, MD,
Pompiliu Ionescu, MD, James E. Caldwell, MB, ChB, Edmond I. Eger II, MD,
Ira J. Rampil, MD, and Stephen H. Lockhart, PhD, MD

Departments of Anesthesia and Physiology and the Cardiovascular Research Institute, University of California, San Francisco, California, and the Department of Anesthesiology, The Jikei University School of Medicine, Tokyo, Japan

We asked if desflurane with or without nitrous oxide at 0.83, 1.24, and 1.66 MAC prevented cardiovascular responses to stimulation. We measured cardiac output, heart rate, systemic arterial blood pressure, central venous pressure, pulmonary arterial blood pressure, and systemic vascular resistance in six healthy male volunteers before (control) and at 0, 1, 2, 4, and 6 min after tetanic electrical stimulation (50, 100, and 200 Hz) of the ulnar nerve. At 0.83 and 1.24 MAC, cardiac output, mean systemic arterial blood pressure, heart rate, and pulmonary arterial blood pressure increased. Peak changes averaged 13%–20% and most frequently occurred 0–2 min after stimulation ($P < 0.05$) with return to control values at 4–6 min (except for pulmonary arterial blood pressure). At 1.66 MAC, heart rate and systemic blood pressure responses were attenuated, but this level of anesthesia had equivocal effects on the cardiac output and pulmonary blood pressure responses. The addition of nitrous oxide attenuated the peak response of heart rate and cardiac output but not the peak response of mean systemic arterial blood pressure. In summary, 0.83 and 1.24 MAC desflurane did not abolish cardiovascular responses to stimulation, but 1.66 MAC attenuated the responses.

(Anesth Analg 1991;73:175–9)

Although the anesthetic state produces immobility and amnesia, it may not abolish primitive responses to the stimulation imposed by surgery. Blood pressure and heart rate may increase, putting stress on the cardiovascular system, a potentially untoward effect in patients with coronary artery disease. Thus, the capacity to abolish or attenuate such responses would be desirable in an anesthetic and might suggest analgetic properties.

Desflurane is a new inhaled anesthetic with attributes that include low solubility in blood and tissues (providing more rapid washin, washout, and recovery than found with present potent agents) (1–3), minimal metabolism (and little or no toxicity) (4–6), and most, if not all, of the advantageous properties of isoflurane, the most widely used potent inhaled anesthetic in North America. Desflurane has the same structure as isoflurane, except for substitution of a fluorine for the chlorine atom in isoflurane. Both anesthetics produce similar changes in circulation, ventilation, and brain activity (as indicated by electroencephalography) in animals and humans.

To assess the capacity of desflurane to attenuate or abolish cardiovascular responses, we studied volunteers' responses to a reproducible level of stimulation at several levels (MAC multiples) of anesthesia. The present report details our assessment. We chose to study volunteers rather than patients because the level of stimulation could be controlled and repeated to give dose-response relationships in a single individual. This is not possible in patients because of the varying level of stimulation supplied by surgery and because of the various levels of anesthesia needed during surgery.

Methods

With approval from the University of California, San Francisco Committee on Human Research and informed consent, we studied six young (24 ± 2 yr, mean ± SD) healthy, fasting male volunteers. Subjects lay supine on a contoured operating table and were given local anesthesia, after which we inserted catheters into a peripheral vein, the left radial artery,

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Supported in part by Anaquest, Inc., and the Anesthesia Research Foundation.

Accepted for publication September 25, 1990.

Address correspondence to Dr. Eger, Room S-455, Box 0464, University of California, San Francisco, CA 94143-0464.

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0003-2999/91/$3.50

Table 1. Control Values

	Oxygen			Nitrous oxide		
Variable	0.83 MAC	1.24 MAC	1.66 MAC	0.83 MAC	1.24 MAC	1.66 MAC
CO	6.11 ± 0.28	6.41 ± 0.50	7.95 ± 0.49	6.50 ± 0.49	6.25 ± 0.55	6.05 ± 0.51
HR	80 ± 2	85 ± 1	102 ± 5	79 ± 4	81 ± 3	81 ± 4
MSAP	61 ± 1	60 ± 1	55 ± 3	69 ± 2	65 ± 2	60 ± 2
MPAP	13 ± 1	15 ± 1	20 ± 1	14 ± 0	16 ± 1	20 ± 1
CVP	6 ± 1	7 ± 1	10 ± 0	6 ± 1	7 ± 1	8 ± 1
SVR	730 ± 50	680 ± 60	470 ± 30	800 ± 70	770 ± 70	670 ± 50

CO, cardiac output (L/min); HR, heart rate (beats/min); MSAP, mean systemic arterial blood pressure (mm Hg); MPAP, mean pulmonary arterial blood pressure (mm Hg); CVP, central venous pressure (mm Hg); SVR, systemic vascular resistance (dyne·s·cm^{-5}).

Control values at each level of anesthesia with and without nitrous oxide. Values are expressed as the mean (±SE). n = 6 for all variables.

and the pulmonary artery. Pressures were transduced (Gould Statham 23XL) from both arterial catheters and the signal recorded (Gould ES2000). We then induced anesthesia by inhalation of desflurane in oxygen or in 60% nitrous oxide, and placed an endotracheal tube without facilitation by muscle relaxants. Ventilation was controlled to maintain normocapnea. Temperature was monitored from a transducer in the pulmonary artery catheter and maintained within 0.3°C of the awake temperature using a Bair Hugger forced-air warmer (Augustine Medical, Inc., Eden Prairie, Minn.).

Half of the volunteers were randomly assigned to receive 0.83, 1.24, and 1.66 MAC (6%, 9%, and 12%) (7) desflurane in oxygen, and the other half 3%, 6%, and 9% desflurane with nitrous oxide to achieve approximately the same MAC multiples. Desflurane and nitrous oxide end-tidal concentrations were measured by infrared analysis (Datex 254). Assignment to 0.83 and 1.24 MAC was randomly ordered, and, for reasons of safety, it always preceded administration of 1.66 MAC. When this dose sequence was completed, it was repeated in both groups, using the alternative background gas (oxygen or nitrous oxide/oxygen).

Anesthesia was maintained at each level for more than 20 min, after which we took baseline measurements of heart rate, mean systemic and pulmonary arterial blood pressures, central venous pressure, and cardiac output. Cardiac output was measured by thermodilution in duplicate, and the measurements were averaged to give a control value unless these values differed by more than 5%. If such a difference existed, the determination was repeated until successive values agreed within 5%. The values agreeing within 5% were averaged to give the control value. Systemic vascular resistance was calculated as (BP − CVP)/Q_t, where BP is blood pressure, CVP is central venous pressure, and Q_t is cardiac output.

After recording control values, we applied 5-s bursts of supermaximal tetanic stimuli (Digistim II) at 50, 100, and 200 Hz, via subcutaneous needle electrodes, to the ulnar nerve at the wrist. Tetanic stimulation was not applied to awake subjects because of the painful nature of the stimulation. These bursts were delivered consecutively at intervals of 10 s. The stimulus was of sufficient magnitude to produce a maximal contraction of the thenar muscles. The above cardiovascular measurements were repeated at the termination of the 200-Hz stimulation, and 1, 2, 4, and 6 min later. However, cardiac output was measured only once at each point because the short intervals between measurements did not permit duplicate determinations.

We calculated the means and variances for the control data, and calculated the change from control as a percentage of the control values. The data were analyzed by analysis of variance with repeated measures and Student-Newman-Keuls test for multiple comparisons. Regression analysis of the peak responses of cardiovascular variables was performed between desflurane with oxygen and desflurane with nitrous oxide anesthesia for data from each subject at each MAC multiple measured (i.e., 0.83, 1.24, and 1.6 MAC). We accepted $P < 0.05$ as significant.

Results

At 0.83 and/or 1.24 MAC, values for systemic arterial blood pressure, heart rate, cardiac output, and pulmonary arterial blood pressure increased from control values (Table 1) with stimulation (Figures 1 and 2). The results at 1.24 MAC usually did not differ from those at 0.83 MAC. Peak changes usually occurred 0–2 min after cessation of stimulation, with all but pulmonary arterial pressure values returning to control within 4–6 min. Individual volunteer responses were variable, as indicated by the large error bars surrounding each mean value.

At 1.66 MAC, only pulmonary arterial pressure increased, and total systemic resistance transiently decreased at 4–6 min. Attenuation of systemic arterial and heart rate responses was most apparent in subjects that had marked responses at 0.83 and/or 1.24

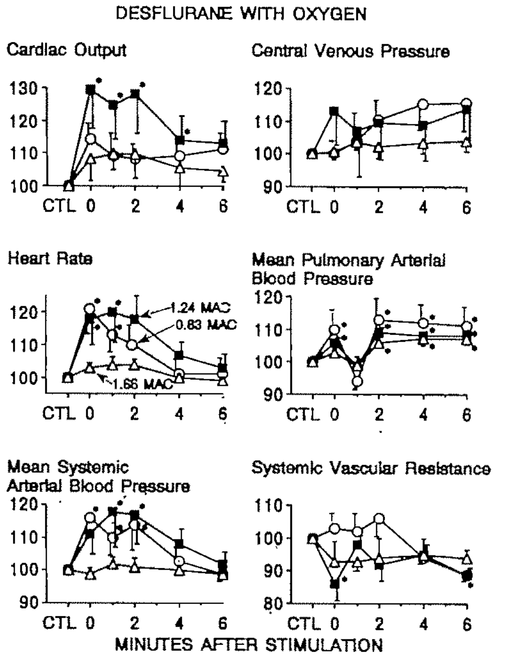

Figure 1. Stimulation of the ulnar nerve tended to increase cardiac output, heart rate, systemic arterial blood pressure, and pulmonary arterial blood pressure above the values immediately before stimulation (ordinate indicates the percentage of that value) during 0.83 (○) and 1.24 (■) MAC but not 1.66 (△) MAC desflurane anesthesia in oxygen ($n = 6$). Except for pulmonary artery blood pressure, values returned to control levels within 6 min after stimulation. CTL, control; values represent percentage of control and are expressed as mean ± SEM. *Significance versus control ($P < 0.05$).

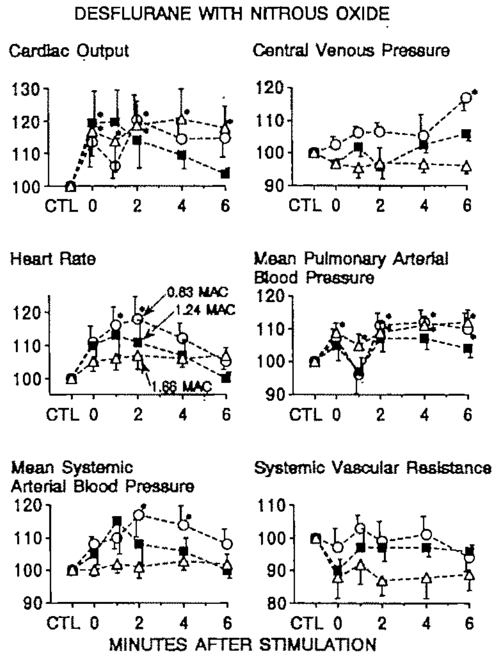

Figure 2. Tetanic stimulation of the ulnar nerve tended to increase cardiac output, heart rate, systemic arterial blood pressure, and pulmonary arterial blood pressure during 0.83 (○), 1.24 (■), and 1.66 (△) MAC desflurane anesthesia in nitrous oxide and oxygen ($n = 6$). These responses were attenuated at 1.66 MAC. The addition of nitrous oxide had no effect (compare Figures 1 and 2). CTL, control; values represent percentage of control and are expressed as mean ± SEM. *Significance versus control ($P < 0.05$).

MAC, but was less consistent in subjects who did not have marked responses at the lighter levels of anesthesia (Figure 3). For desflurane in oxygen, the increases in heart rate and arterial blood pressure at 0.83 and 1.24 MAC differed significantly ($P < 0.05$) from the changes (nonsignificant) in rate and pressure found at 1.66 MAC. For desflurane in nitrous oxide, the increase in pressure seen at 0.83 MAC was significantly ($P < 0.05$) less than the change found at 1.66 MAC. Attenuation of the peak mean arterial blood pressure responses appeared to be independent of the presence of nitrous oxide (Figure 3). Central venous pressure, pulmonary arterial pressure, and total systemic resistance responses in relation to anesthetic level varied among subjects and, except for the pulmonary arterial pressure response, usually did not differ from control values.

Correlation of peak responses to stimulation between desflurane with oxygen anesthesia and desflurane with nitrous oxide was significant for systemic arterial pressure ($r^2 = 0.73$; $P < 0.001$) and heart rate ($r^2 = 0.50$; $P < 0.001$) but not for cardiac output ($r^2 = 0.19$; $P = 0.072$), central venous pressure, pulmonary arterial pressure, and systemic vascular resistance (Figures 4 and 5). The regression of the peak response of mean systemic arterial blood pressure during anesthesia with versus without nitrous oxide had a slope of 0.91 ± 0.14 (mean ± SD). However, the slopes for heart rate (0.56 ± 0.14) and cardiac output (0.33 ± 0.17) were less than 1.0, indicating a diminished peak response in the presence of nitrous oxide.

Discussion

Our results indicate that neither 0.83 nor 1.24 MAC desflurane, with or without nitrous oxide, abolished the circulatory response to supramaximal tetanic stimulation of the ulnar nerve, or caused a dose-related attenuation of this response. The lack of a dose-related attenuation of this response was also observed with enflurane in a study by Roizen et al. (8). However, Roizen et al. reported that halothane alone and nitrous oxide with narcotic do abolish these responses to skin incision in a dose-dependent manner. Our study differed from theirs in the type (electrical vs surgical) and duration (transient vs continuing) of stimulation, the criterion for circulatory response (ours was any significant increase and theirs a 10% or greater change in response), and patient age (ours was younger).

We also evaluated circulatory responses to 1.66 MAC

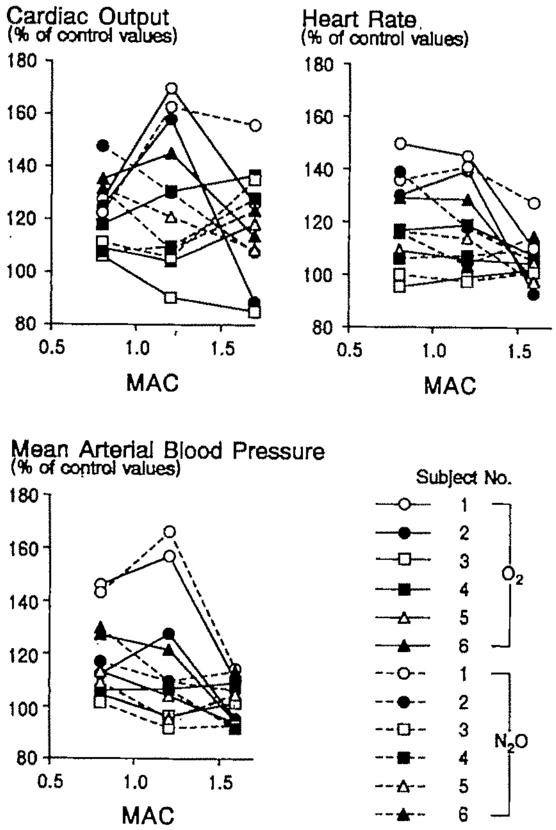

Figure 3. Individual peak percentage changes in cardiac output, heart rate, and systemic arterial blood pressure are plotted against MAC multiples. *Solid lines* indicate data for desflurane with oxygen and *dashed lines* desflurane with nitrous oxide. Heart rate and systemic arterial blood pressure responses were attenuated at 1.66 MAC in subjects who had marked responses at 0.83 and/or 1.24 MAC, regardless of the presence of nitrous oxide.

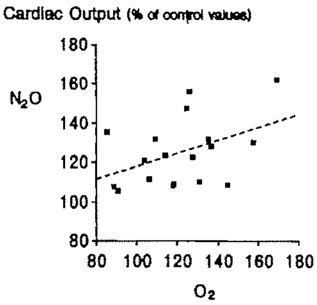

Figure 4. Peak cardiac output responses to stimulation were less with desflurane in the presence of nitrous oxide than in the presence of oxygen ($y = 18 + 0.33x$, $r^2 = 0.18$). However, the relationship was not significant ($P = 0.072$).

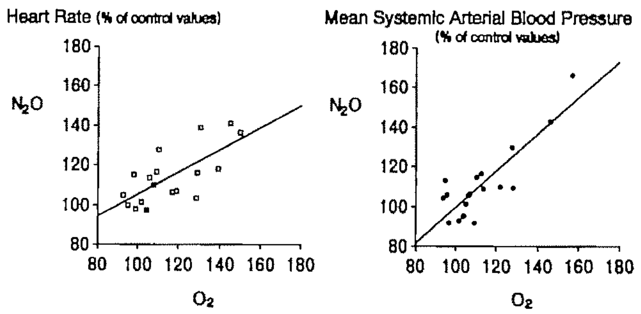

Figure 5. Peak heart rate and systemic arterial blood pressure responses to stimulation during anesthesia with desflurane in oxygen correlated with the peak responses during anesthesia with desflurane in nitrous oxide (for heart rate, $y = 5.2 + 0.56x$, $r^2 = 0.50$, $P < 0.001$; for systemic arterial blood pressure, $y = -0.11 + 0.91x$, $r^2 = 0.73$, $P < 0.001$). The addition of nitrous oxide may attenuate heart rate responses but has little effect on systemic arterial blood pressure responses.

desflurane and found no response other than an increase in cardiac output and mean pulmonary arterial blood pressure in the presence of nitrous oxide. However, control values for heart rate and cardiac output at 1.66 MAC in oxygen were higher than values obtained at 0.83 and 1.24 MAC in oxygen, indicating the presence of stimulation from the anesthetic itself (Table 1). An increased baseline value would limit the chance of finding a significant response to stimulation because an increased baseline value would (a) result in a smaller percentage increase for a given absolute change; and (b) limit the absolute increase possible as the baseline value approached the maximum possible level of activity. In contrast to this limitation to the interpretation of the desflurane-oxygen results, the absence of an increase in control values for these variables in the presence of nitrous oxide may reflect a real attenuation of the responses, indicating that MAC-BAR for this combination lies between 1.24 and 1.66 MAC.

The increases in heart rate, blood pressure, and cardiac output during desflurane anesthesia with oxygen are similar to those observed after administration of norepinephrine or epinephrine or direct stimulation of sympathetic outflow, including the cardioaccelerator nerves. Moreover, we observed a tendency toward vasodilation during recovery from stimulation; that is, systemic vascular resistance decreased at 4–6 min. Thus, cardiovascular responses to desflurane appear to be mediated by the sympathetic nervous system.

The increases in mean systemic arterial blood pressure in response to stimulation varied widely among subjects (Figures 3 and 5) but for a given subject were consistent (Figure 5). A similar, but less uniform, result was seen for heart rate and a still less uniform result for cardiac output (Figures 3 and 4). These findings suggest that intersubject differences determine the variability of the responses in blood pressure and that nitrous oxide does not attenuate these responses, whereas deeper levels of anesthesia do provide attenuation. In contrast, it appears that nitrous oxide does attenuate the heart rate and cardiac output responses (which are not completely independent because of the impact of heart rate on output). However, in the presence of nitrous oxide, deeper levels of anesthesia decrease the heart rate but not the output responses.

Our results indicate that 0.83 or 1.24 MAC desflurane alone (or with nitrous oxide) may not protect patients at risk of myocardial ischemia from increased myocardial oxygen demand secondary to surgical stimulation. However, the responses to surgical stimulation may differ from those we found. Additionally, the cardiovascular responses in our young volunteers may be greater than those in older patients (i.e., those most at risk of myocardial ischemia). Moreover, the addition of narcotics to an anesthetic regimen including desflurane might provide an element of analgesia that would attenuate or abolish the response to stimulation. This advantageous property of narcotics is widely used to enhance the quality of anesthesia achieved with isoflurane. Similarly, Roizen et al. demonstrated that the use of morphine with enflurane can abolish the response to skin incision (8).

Finally, ongoing surgical stimulation may elicit differing cardiovascular responses to desflurane. Most of the responses we observed returned to control levels 4–6 min after the cessation of stimulation, possibly because of the absence of stimulation or of an adaptation to stimulation. If adaptation occurs, ongoing surgical stimulation may induce less cardiovascular change (after an initial response) than our peak changes would indicate. Alternatively, ongoing surgical stimulation without adaptation might provoke greater and more prolonged responses.

We gratefully acknowledge Winifred von Ehrenburg, MA, for her editorial assistance. We would like to thank Augustine Medical, Inc., for donating the Bair Hugger forced air warmer.

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Fluoride Metabolites After Prolonged Exposure of Volunteers and Patients to Desflurane

Trevor S. Sutton, AB, Donald D. Koblin, PhD, MD, Larry D. Gruenke, PhD,
Richard B. Weiskopf, MD, Ira J. Rampil, MD, Lucy Waskell, MD, PhD, and
Edmond I. Eger II, MD

Department of Anesthesia, Veterans Administration Medical Center, San Francisco, and the Department of Anesthesia, University of California, San Francisco, California

We examined the metabolism of desflurane in 13 healthy volunteers given 7.35 ± 0.81 MAC-hours (mean ± SD) of desflurane and 26 surgical patients given 3.08 ± 1.84 MAC-hours (mean ± SD). Markers of desflurane metabolism included fluoride ion measured via an ion-specific electrode, nonvolatile organic fluoride measured after sodium fusion of urine samples, and trifluoroacetic acid determined by a gas chromatographic-mass spectrometric method. In both volunteer and patient groups, postanesthesia serum fluoride ion concentrations did not differ from background fluoride ion concentrations. Similarly, postanesthesia urinary excretion of fluoride ion and organic fluoride in volunteers was comparable to preanesthesia excretion rates. However, small but significant levels of trifluoroacetic acid were found in both serum and urine from volunteers after exposure to desflurane. A peak serum concentration of 0.38 ± 0.17 μmol/L of trifluoroacetic acid and a peak urinary excretion rate of 0.169 ± 0.107 μmol/h were detected in volunteers at 24 h after desflurane exposure. Although these increases in trifluoroacetic acid after exposure to desflurane were statistically significant, they are approximately 10-fold less than levels seen after exposure to isoflurane. Thus, desflurane strongly resists biodegradation, but a small amount is metabolized in humans.

(Anesth Analg 1991;73:180–5)

Desflurane (formerly I-653) is a new volatile anesthetic that differs from isoflurane by substitution of a fluorine atom for a chlorine atom. This single change results in a compound that is less soluble, permitting a rapid recovery from anesthesia in rats (1) and in swine (2). Thus desflurane may have an advantage over presently used anesthetics in operations where rapid recovery from anesthesia is desirable.

The substitution of a fluorine atom for a chlorine atom also appears to have produced a more stable compound. In vitro, this is reflected in an increased resistance to degradation by soda lime, particularly at increased temperatures (3). In vivo, it is reflected as a resistance to metabolism in animals (4,5). Indeed, the only demonstration of metabolism was a slight increase in serum inorganic fluoride immediately after anesthesia or a slight increase in urinary excretion in the 24 h after anesthesia in enzyme-induced rats (4). Humans given about 1 MAC-hour of anesthesia with desflurane do not have increases in serum or urinary fluoride (6).

The issue of metabolism of desflurane is of interest because of the potential connection between metabolism and toxicity. The absence of metabolism, or a metabolism markedly less than that obtained with other anesthetics, would be an added advantage of desflurane. Although the previous studies in humans have not revealed metabolism, they may not have constituted a sufficient test because of the limited duration and concentration of desflurane that was applied. The present report gives data for prolonged exposure to desflurane at sometimes high concentrations in both volunteers and patients, and in addition examines for trifluoroacetic acid, a more sensitive marker of desflurane metabolism that was not assayed in previous studies of desflurane metabolism in humans (6).

Methods

Subjects

This study was approved by the University of California, San Francisco, Committee on Human Research, and all participants (subjects) gave informed

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Supported in part by Anaquest and Anesthesia Research Foundation.

Accepted for publication October 9, 1990.

Address correspondence to Dr. Koblin, Anesthesiology Service (129), Veterans Administration Medical Center, 4150 Clement Street, San Francisco, CA 94121.

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0003-2999/91/$3.50

consent. Thirteen ASA physical status I male volunteers, aged 19–26 yr and of normal body weight for their height, were studied. These volunteers were concomitantly examined for the cardiovascular, respiratory, and neuromuscular effects of desflurane (7–9). No volunteers drank more than six alcoholic drinks per week on average, and all abstained from all alcohol and over-the-counter medications during the 48 h before study. Candidates taking acetaminophen within 48 h of the study, with a history of a positive test for hepatitis B surface antigen or HIV antibody, with abnormal serum alanine transaminase activity, or with a history of unusual response to anesthesia or exposure to anesthesia within 3 mo of the study, were excluded. Candidates with a history of parenteral drug abuse, and candidates taking antiinflammatory drugs, antihistamines, or antibiotics within 1 wk of the study, were excluded.

Twenty-six ASA physical status I and II male surgical patients, aged 21–63 yr, were also studied. These patients were concomitantly examined for determination of the MAC of desflurane (10). These patients had elective orthopedic, otolaryngologic, neurosurgical, or general surgical operations. None were obese (weight range, 51–95 kg), and none had known preoperative abnormalities in hepatic function. None of the patients had a history of alcohol abuse. None of the patients received chronic medications that are known to alter the metabolism of volatile anesthetics. None of the patients ever had an adverse reaction to an anesthetic.

Exposure to Desflurane

Volunteers were anesthetized with desflurane at the concentrations and durations required to concomitantly study cardiovascular (7), respiratory (8), and neuromuscular (9) effects of desflurane. Volunteers were given desflurane for 6.81 ± 0.55 h (±SD), and the total dose of desflurane was 7.35 ± 0.81 MAC-hours. Surgical patients were given desflurane at the concentrations and durations needed to concomitantly determine the MAC of desflurane (10). Surgical patients received desflurane for 3.40 ± 2.07 h and the total dose of desflurane was 3.08 ± 1.84 MAC-hours (mean values ± SD).

Collection of Urine and Serum Samples

Urine samples were collected from volunteers 7–10 days before exposure to desflurane, at the end of exposure, and at 24 h, 4 days, and 6 days after exposure. All urine samples were collected over a 12-h period (7 PM to 7 AM) with the exception of the end-of-anesthesia collections, which were collected over the period of exposure to anesthesia plus the initial recovery period (a total of 7–10 h). Total urine volumes were recorded for each interval.

Arterial blood samples from volunteers were collected 7–10 days before desflurane exposure, immediately before induction with desflurane, at the end of exposure, and at 4 h, 24 h, 4 days, and 6 days after discontinuing desflurane. In surgical patients, blood was collected immediately before operation, in the postanesthesia recovery room, and less frequently at 1 and 3 days after operation. Urine was not collected from the surgical patients.

Serum was isolated from blood after centrifugation at 2000 *g* for 10 min. Serum and urine samples were placed in plastic test tubes and kept frozen at −20 to −40°C before analysis for fluoride and trifluoroacetate.

Fluoride Analyses

Fluoride ion levels in serum and urine were determined using a modified method of Fry and Taves (4,11). Twenty microliters of a 5 M sodium acetate buffer (pH 4.50) was added to 180 μL of undiluted serum or to 180 μL of a urine sample previously diluted fourfold. The 200-μL mixture was placed into a machined Teflon cup, and the fluoride ion concentration was measured using an Orion fluoride ion electrode (model 96-09) with a Corning model 12 pH meter. Fluoride ion concentrations in serum or urine were obtained by interpolation of a calibration curve prepared by plotting electrode voltage on a linear scale against the concentration of sodium fluoride standards on a logarithmic scale.

The content of total fluoride in the urine was determined by the sodium fusion method of Soltis and Gandolfi (4,12). Nonvolatile organic fluoride from urine samples was calculated by subtracting the free fluoride ion in the original sample from the total fluoride content determined by the sodium fusion technique, after correction for the efficiency of organic fluoride detection. We assumed a 90.4% recovery of organic fluoride based on results from earlier studies (13).

Trifluoroacetic Acid Analysis

Trifluoroacetic acid levels in the serum and urine collected from volunteer subjects were determined by the gas chromatographic-mass spectrometric method of Gruenke and Waskell (14), using pentafluoropropionic acid as the internal standard. The limit of detection of trifluoroacetic acid using this method ranged between concentrations of 0.10 and 0.20 μmol/L.

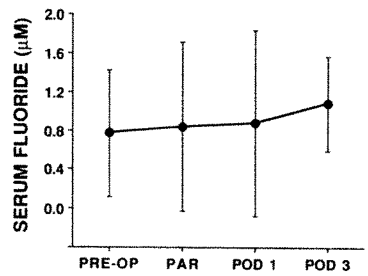

Figure 1. Serum fluoride ion concentrations in patients anesthetized with desflurane (3.08 ± 1.84 MAC-hours). Values were obtained immediately before the operation (PRE-OP; $n = 26$), in the postanesthesia recovery room (PAR; $n = 25$), and on postoperative days (POD) 1 ($n = 15$) and 3 ($n = 5$). Error bars indicate ±SD. There was no statistically significant change between preanesthesia and postanesthesia concentrations of serum fluoride ion.

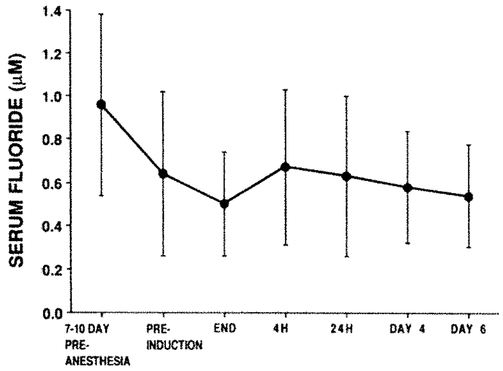

Figure 2. Serum fluoride ion concentrations in volunteers anesthetized with desflurane (7.35 ± 0.81 MAC-hours). Values were obtained at 7–10 days before anesthesia ($n = 12$), immediately before anesthesia ($n = 13$), at the end of anesthesia ($n = 8$), and at 4 h ($n = 12$), 24 h ($n = 13$), 4 days ($n = 13$), and 6 days ($n = 13$) after anesthesia. Error bars indicate ±SD. There was no statistically significant change between preanesthesia and postanesthesia concentrations of serum fluoride ion.

Statistical Analysis

Comparisons between values obtained before and after desflurane exposure were performed by a paired, two-tailed *t*-test. We accepted *P* values of less than 0.05 as significant, after using the Bonferroni correction for multiple comparisons. Values are expressed as mean ± SD.

Results

In both patients (Figure 1) and volunteers (Figure 2), postanesthesia serum fluoride ion concentrations did not significantly exceed background fluoride ion concentrations. Urinary excretion of fluoride ion and organic fluoride in volunteers also did not significantly increase after exposure to desflurane (Figure 3).

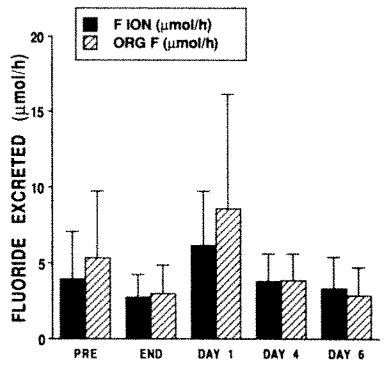

Figure 3. Urinary excretion rates of fluoride ion and organic fluoride in volunteers anesthetized with desflurane (7.35 ± 0.81 MAC-hours). Values were obtained 7–10 days before anesthesia ($n = 11$), at the end of anesthesia ($n = 5$), and at 24 h ($n = 13$), 4 days ($n = 13$), and 6 days ($n = 12$) after anesthesia. Error bars indicate ±SD. There was no statistically significant change between preanesthesia and postanesthesia urinary excretion rates of either fluoride ion or organic fluoride.

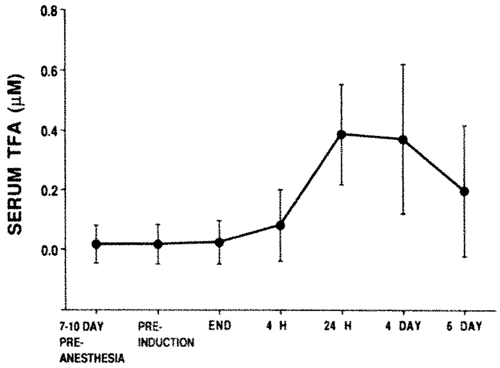

Figure 4. Serum trifluoroacetic acid concentrations in volunteers anesthetized with desflurane (7.35 ± 0.81 MAC-hours). Values were obtained 7–10 days before anesthesia ($n = 12$), immediately before induction with anesthetic ($n = 13$), at the end of anesthesia ($n = 9$), and at 4 h ($n = 11$), 24 h ($n = 13$), 4 days ($n = 13$), and 6 days ($n = 13$) after anesthesia. Error bars indicate ±SD. Trifluoroacetic acid levels were significantly elevated and maximal (0.38 ± 0.17 µmol/L) at 24 h after anesthesia. These concentrations remained significantly elevated above background at 6 days after desflurane anesthesia.

Trifluoroacetic acid appeared in the serum of volunteers exposed to desflurane (Figure 4). Serum trifluoroacetic acid levels were significantly elevated 24 h after desflurane exposure and remained elevated (in 6 of 13 volunteers with values of 0.21, 0.22, 0.43, 0.49, 0.52, and 0.52 µmol/L) 6 days after desflurane exposure (Figure 4). Urinary excretion of trifluoroacetic acid increased significantly above a nondetectable background rate in volunteers (Figure 5). This increase was detected in four volunteers immediately after desflurane anesthesia and was found in all individuals 24 h after anesthesia. Urinary excretion of trifluoroacetic acid was maximal 24 h after desflurane anesthesia and was still evident 6 days after anesthesia (Figure 5).

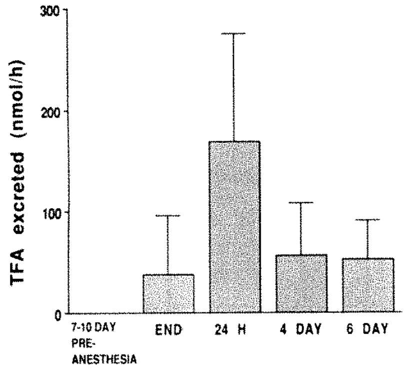

Figure 5. Urinary excretion rates of trifluoroacetic acid in volunteers anesthetized with desflurane. Values were obtained at 7–10 days before anesthesia ($n = 12$), at the end of anesthesia ($n = 7$), and at 24 h ($n = 13$), 4 days ($n = 13$), and 6 days ($n = 11$) after anesthesia. Error bars indicate ±SD. The excretion rate of trifluoroacetic acid was significantly elevated above background at the end of anesthesia. The excretion rate was maximal (0.169 ± 0.107 μmol/h) at 24 h after anesthesia and remained significantly increased at 6 days after anesthesia.

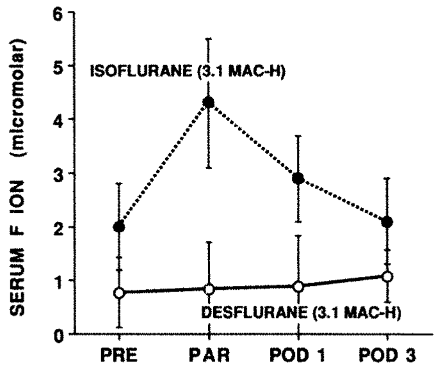

Figure 6. Serum fluoride ion concentrations in patients anesthetized with desflurane in the present study are compared with results from a previous study (18) where patients were anesthetized with isoflurane. Error bars indicate ±SD. Levels of fluoride ion in serum were increased above background concentrations after exposure to isoflurane. There was no significant increase in serum fluoride ion concentrations after exposure to desflurane. (Pre = before anesthesia, PAR = postanesthesia recovery, POD = postoperative day).

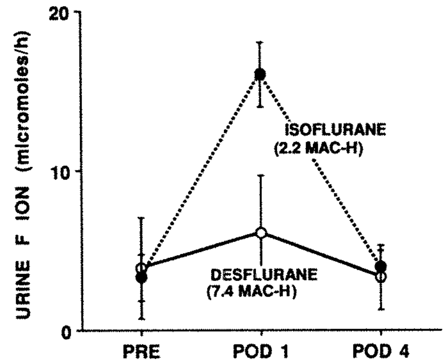

Figure 7. Urinary excretion rates of fluoride ion in volunteers in the present study are compared with results from a previous study (25) where patients were anesthetized with lower average doses of isoflurane. Error bars indicate ±SD. The excretion rate of fluoride ion increased above the background excretion rate after exposure to isoflurane. There was no significant increase in the urinary excretion rate of fluoride ion after exposure to desflurane.

Discussion

Because desflurane closely resembles isoflurane in chemical structure, we expected that if desflurane was metabolized, its route and products of metabolism would resemble those of isoflurane. Isoflurane metabolism has been previously described to involve breakdown by cytochrome P450 to yield either an active acylating agent (CF_3COF or $CF_3COOCHF_2$) or trifluoroacetaldehyde, in addition to a one-carbon fragment (15). Based on results from previous investigations, trifluoroacetaldehyde is largely converted to trifluoroacetate in humans (16,17). Thus, if desflurane is metabolized similarly to isoflurane, by either route it would be expected to yield 1 mol of trifluoroacetate and 2 mol of fluoride ion for each mole metabolized.

In the current study we examined desflurane metabolism in humans by comparing pre- and postanesthesia levels of fluoride ion and organic fluoride (specifically trifluoroacetate) in the urine of volunteers and in the serum of volunteers and patients anesthetized with this drug. Our results in humans are consistent with results from earlier studies in rats (4) and in swine (5), and suggest that although desflurane strongly resists biodegradation, a small amount is metabolized. Mean serum fluoride ion concentrations in volunteers after exposure to 7.35 ± 0.81 MAC-hours of desflurane failed to rise above a mean 7–10-day preexposure serum fluoride ion concentration of 0.96 ± 0.42 μmol/L. In surgical patients exposed to 3.08 ± 1.84 MAC-hours of desflurane, mean postexposure serum fluoride ion concentrations did not significantly rise above a mean preanesthesia serum fluoride ion concentration of 0.77 ± 0.65 μmol/L. Similarly, the excretion rate of fluoride ion and organic fluoride in the urine of volunteers after exposure to desflurane did not exceed preexposure excretion rates. The present data contrast with elevated concentrations of fluoride ion in serum (Figure 6) and fluoride ion and organic fluoride in urine (Figures 7 and 8) of surgical patients after exposure to isoflurane (18). In this study of Mazze et al. (18), ASA I patients were given isoflurane at concentrations of 0.5–1.0 MAC for 2.0–7.5 h for a total dose of 3.1 MAC-hours. Mean peak serum concentrations of fluoride ion were 4.4 μmol/L measured 6 h after isoflurane anesthesia (18). Thus, higher concentrations of fluoride ion in serum were found after anesthesia with isoflurane, even though lower average doses of isoflurane than desflurane were admin-

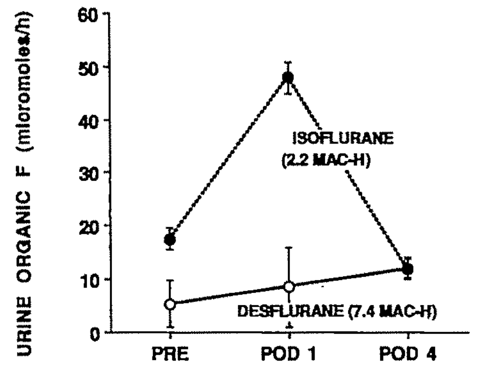

Figure 8. Urinary excretion rates of organic fluoride in volunteers anesthetized with desflurane in the present study are compared with results from a previous study (25) where patients were anesthetized with lower average doses of isoflurane. In the isoflurane study, urinary organic fluoride was identified by combustion of a spot that comigrated with trifluoroacetic acid on a thin-layer chromatograph. Error bars indicate ±SD. The excretion rate of organic fluoride increased above the background excretion rate after exposure to isoflurane. There was no significant increase in the urinary excretion rate of organic fluoride after exposure to desflurane.

istered. Although there are limitations in comparing fluoride levels measured in separate studies, these findings suggest that desflurane resists biodegradation more than isoflurane, the agent that is the least metabolized of the currently available inhalation anesthetics (19).

Mean serum trifluoroacetic acid concentrations and mean urine trifluoroacetic acid excretion rates in volunteers at 24 h, 4 days, and 6 days after exposure to desflurane were significantly elevated, with a peak mean serum concentration of 0.38 μmol/L at 24 h. This serum trifluoroacetic acid concentration after desflurane anesthesia is approximately 1000-fold lower than the concentration of about 500 μmol/L achieved after the administration of 0.44%–1.57% end-expired halothane for 2 h to patients having intraabdominal surgery (20). Comparison with isoflurane is difficult because only limited data are available for trifluoroacetic acid production after isoflurane administration to patients. In individuals who have received isoniazid, peak serum concentrations are on the order of 10 μmol/L after isoflurane anesthesia (13). The peak mean excretion rate of trifluoroacetic acid in urine after exposure to desflurane (0.169 μmol/h) (Figure 5) is about 100-fold less than that observed after exposure of patients to lower average doses of isoflurane (approximately 50 μmol/h) (18).

Our finding that trifluoroacetic acid levels increase slightly above background after exposure of volunteers to desflurane demonstrates that a small degree of metabolism does occur. That the degree is small presumes that the extent of anesthetic metabolism is proportional to the serum fluoride ion, organic fluoride, and trifluoroacetic acid concentrations. Although this assumption is probably reasonable, it is possible that higher levels of metabolites might have been disclosed if we had made more frequent measurements or if before anesthesia our subjects had taken drugs or medications that induce synthesis of hepatic microsomal enzymes (21). Furthermore, it remains possible that fluoride ion could be sequestered (e.g., in bone or liver) and not appear in blood, or that breakdown products are excreted via the lungs rather than in serum or in urine. However, mass balance studies performed in human volunteers demonstrate a recovery of desflurane of 100% (22), a value not significantly different from that seen with isoflurane.

The low levels of fluoride metabolites in serum and urine after desflurane anesthesia suggest that desflurane is unlikely to be toxic to tissues. Although trifluoroacetic acid metabolites were detected, and a theoretical potential for desflurane hepatotoxicity by cross-sensitivity with other inhalation anesthetics cannot be excluded (23,24), the possibility appears to be remote. Such a possibility has yet to be demonstrated for isoflurane. The conversion of isoflurane to trifluoroacetate and other fluoride metabolites is small, amounting to an estimated 0.17% of the isoflurane taken up (19). If the peak serum trifluoroacetate values indicate the relative amounts of metabolism, then probably less than 0.02% of the amount of desflurane taken up is metabolized. This figure is arrived at by multiplying the ratio of peak serum trifluoroacetate (0.38/10) times the ratio of blood/gas partition coefficients (1.4/0.42—used to compensate for differences in uptake) times the 0.17% value cited earlier.

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Serum Levels of Hyskon During Hysteroscopic Procedures

Devanand Mangar, MD, John I. Gerson, MD, Michael S. Baggish, MD, and Enrico M. Camporesi, MD

Department of Anesthesiology, University of South Florida College of Medicine, Tampa, Florida and Departments of Anesthesiology and of Obstetrics and Gynecology, SUNY-Health Science Center, Syracuse, New York

Hyskon hysteroscopy fluid is used with the hysteroscope as an aid in distending the uterine cavity and in visualizing its surfaces. We correlated the amount of Hyskon used during hysteroscopy with both the instillation pressures generated within the uterine cavity and with serum levels of Hyskon in 11 healthy subjects. Serum levels in excess of 1000 mg% were measured at 30 min when an amount of Hyskon greater than 300 mL was used. Intrauterine Hyskon absorption and/or injection during hysteroscopy were found even after volumes of Hyskon as small as 50–100 mL were used. Serum levels were significantly higher with the larger amounts of Hyskon used in ablative procedures ($P < 0.01$), as compared with serum levels seen with the smaller amounts of Hyskon used for diagnostic procedures. The injection pressures should be low to minimize the amount of intravascular injection. In cases in which extensive ablative procedures are necessary, we suggest that a two-stage procedure be considered. Because of the hypertonicity of Hyskon, intravascular volume expansion that may be larger than that seen during transurethral prostatectomy occurs.

(Anesth Analg 1991;73:186–9)

Hyskon (32% Dextran-70, Hyskon® Division, Pharmacia, Piscataway, N.J.) hysteroscopy fluid is a clear, viscid, sterile, nonpyrogenic solution of dextran-70 (32% wt/vol) in dextrose (10% wt/vol). Dextran-70 is that fraction of dextran, a branched polysaccharide composed of glucose units, having an average molecular weight of 70,000. The fluid is electrolyte-free and nonconductive. Hyskon is indicated for use with the hysteroscope as an aid in distending the uterine cavity and in irrigating and visualizing its surfaces. Pulmonary edema with and without coagulopathy ascribed to rapid intravascular absorption of this visualizing medium has been described with the use of Hyskon (1–5). It has been recommended (Pharmacia, personal communication, July 1990) that no more than 500 mL of Hyskon be injected at any one time to prevent pulmonary edema. However, no study has been published correlating the amount of Hyskon used with levels of Hyskon in the blood.

In this study, we correlated the amount of Hyskon used during hysteroscopy with the instillation pressures generated within the uterine cavity and with the serum levels of Hyskon. Simultaneously, we measured postoperative bleeding, coagulation variables, serum electrolyte levels, and blood gas tensions to obtain an index of pulmonary function. We believed that Hyskon is absorbed from the endometrium in the same way that fluid is absorbed from the prostatic bed during transurethral prostatectomy.

Methods

Eleven ASA physical status I and II patients who underwent diagnostic and therapeutic (uterine ablation) hysteroscopy under general anesthesia participated in the study. Prior institutional review board approval and patient written informed consent were obtained. All patients had a history of uterine bleeding and were undergoing hysteroscopy for either diagnosis or ablation of endometrium. Patients were screened with preoperative measurements of prothrombin, partial thromboplastin time, thrombin time, fibrin split products, and fibrinogen in addition to routine preoperative laboratory studies.

Anesthesia was induced with intravenous thiopental (4 mg/kg), and tracheal intubation was aided by succinylcholine (1–2 mg/kg); subsequent relaxation was facilitated by atracurium (0.3 mg/kg). Anesthesia was maintained with isoflurane, N_2O-O_2 in a 70%:30% mixture. After the patient was anesthetized, a 22-gauge radial arterial line was inserted. Baseline analysis of arterial blood gases was performed while the patient was breathing a fraction of inspired oxygen of 0.3, and baseline arterial serum Hyskon levels were determined.

Supported by a grant from Pharmacia, Hyskon® Division, Piscataway, New Jersey.

Accepted for publication April 17, 1991.

Address correspondence to Dr. Mangar, University of South Florida College of Medicine, Department of Anesthesiology, 12901 Bruce B. Downs Boulevard, Box 59, Tampa, FL 33612.

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Hysteroscopy was performed by the same gynecologist in all patients, but different assistants injected Hyskon. The injection pressure at the hysteroscope was continuously measured with a Medi-Tech LeVeen inflator (Medi-Tech, Inc., Watertown, Mass.; full scale 0–20 atm) using a three-way stopcock. The intrauterine pressure was intermittently measured by a DTX transducer system (Viggo-Spectramed, Oxnard, Calif.) calibrated in millimeters of mercury, using the same port on the hysteroscope but with the stopcock turned to close off the injection Hyskon syringe. Simultaneous measurement of both pressures was not possible as the hysteroscope had only one port; passing a catheter along the side of the hysteroscope through the cervix would have created a leak and would have compromised visualization. The amount of Hyskon used and the intrauterine pressure were intermittently monitored when the surgical procedure could be halted. Thus, Hyskon injection pressure was monitored during most of the procedure, and intrauterine pressure was monitored only when no injection occurred. Hyskon levels after the beginning of the procedure were measured at 15 and 30 min if the duration of the procedure allowed. The last arterial blood gas tension was measured at the end of the procedure. Coagulation studies were also carried out in all 11 patients at the time of the last Hyskon level. One patient had the serum Hyskon level measured at 4 h.

Blood for Hyskon levels was centrifuged at 2500 rpm for 15 min with a Beckman TJ6 (Beckman Instruments, Inc., Palo Alto, Calif.); the serum was pipetted into a plastic container and sent to Dexall Biomedical Labs, Inc., Gaithersburg, Md., where Hyskon level was assayed by the method of Gabel and Kerkkamp (6). This technique determined Hyskon levels by acid hydrolysis and by partial neutralization of dextran-70. The resulting glucose was determined with the aid of glucose oxidase. Our data report Hyskon levels in milligram percent; there are 320 mg in 1 mL of Hyskon. The volume of Hyskon absorbed into the circulation was calculated assuming a plasma volume of 2500 mL. As 100 mL of Hyskon = 32 g dextran, 1 mL Hyskon = 0.32 g dextran. A Hyskon level of 2000 = 2.0 g/100 mL or 20 g/L. Assuming a plasma volume of 2500 mL, then there would be 50 g of dextran. As 0.32 g of dextran = 1 mL Hyskon, then 50 g dextran = 156 mL Hyskon. Statistical analysis was done by linear regression and by analysis of variance. A probability value less than 0.01 was considered to be significant.

Table 1. Volumes of Hyskon Used and Serum Levels 15 Min After Injection

Patient No.	Procedure	Hyskon used (mL)	Serum Hyskon levels (mg%)	Calculated volumes of Hyskon absorbed (mL)
1	Ablation[a]	410	320	25
2	Ablation	150	480	38
3	Diagnosis	260	25	2
4	Ablation	470	2000	156
5	Ablation	340	1700	133
6	Diagnosis	100	0	0
7	Ablation[a]	360	1600	125
8	Diagnosis	155	52	4
9	Diagnosis	180	5	4
10	Diagnosis	22	0	0
11	Ablation	360	2700	211

[a] Bleeding postoperatively.

Results

None of the hysteroscopies lasted longer than 30 min. Absorption into the bloodstream appeared related to the volume of Hyskon used, the duration of the procedure, and the pressure of uterine distention. The highest serum level observed in this study did not exceed 3000 mg%. Patients who underwent diagnostic procedures had lower serum levels than those who had ablative procedures. In five patients who underwent diagnostic hysteroscopy (Table 1), the use of low Hyskon volumes resulted in serum levels of less than 52 mg% at 15 min ($P < 0.01$) and of 58 mg% in the only patient who received 260 mL at 30 min. In six patients who had ablative procedures, the use of larger volumes ranging from 360 to 480 mL resulted in serum Hyskon levels between 320 and 2700 mg% at 15 min. At 30 min, the Hyskon levels ranged between 460 and 2900 mg% (Table 2). In patient 11 whose Hyskon levels were measured at 30 min, a measurement was again made at 4 h at which time the level was 2800 mg%. In the six patients with high blood levels, two received more than 360 mL during the procedure and had postoperative vaginal bleeding that necessitated placement of an intrauterine balloon and overnight stay in the hospital. Serum Hyskon levels in patients having ablative procedures averaged 1467 ± 913 (SD) mg% and in those having diagnostic procedures, 16.4 ± 22.4 mg%. The coagulation profile in the blood drawn at the time of the last Hyskon level measurement in all patients was normal. Pulmonary edema was not evident in any patient. The percent decrease in sodium ($r = 0.88$, $P = 0.0004$) was in the same direction (although it was much less) as the percent decrease in hematocrit ($r = 0.82$, $P = 0.002$) (Table 3). This decrease may be from the intravenous infusion of 600–1000 mL of saline or lactated Ringer's solution used in these patients as these fluids would decrease hematocrit levels more than serum sodium levels.

Table 2. Volumes of Hyskon Used and Serum Levels 30 Min After Injection

Patient No.	Procedure	Hyskon used (mL)	Serum Hyskon levels (mg%)	Calculated volumes of Hyskon absorbed (mL)
1	Ablation[a]	410	1600	125
2	Ablation	150	460	36
3	Diagnosis	260	58	5
4	Ablation	470	1900	148
5	Ablation	340	1500	117
6	Diagnosis	100	A	A
7	Ablation[a]	360	1900	148
8	Diagnosis	155	A	A
9	Diagnosis	180	A	A
10	Diagnosis	22	A	A
11[b]	Ablation	360	2900	227

A, not measured/termination of procedure.
[a] Bleeding postoperatively.
[b] Four-hour level = 2800 mg% = 218 mL.

Table 3. Hematocrit and Serum Sodium Values Before and After Procedure

	Hematocrit		Na⁺	
Patient No.	Pre (%)	Post (%)	Pre (mEq/L)	Post (mEq/L)
1	36	32	139	137
2	40	38	142	140
3	34	34	143	144
4	40	29	144	135
5	40	35	143	140
6	36	34	142	143
7	43	35	141	137
8	38	36	141	143
9	45	38	142	142
10	42	40	140	143
11	41	32	144	137

In all patients, intraoperative blood loss was less than 50 mL, the mean injection pressures were between 0.5 and 3.9 atm, and the mean intrauterine pressures were between 10 and 160 mm Hg. A significant correlation between pressure and serum Hyskon levels ($r = 0.712$, $P = 0.01$) was seen at 15 min, when Hyskon concentration was plotted against dose (Figure 1).

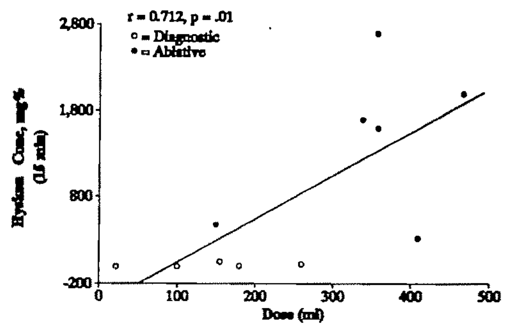

Figure 1. Hyskon concentration and doses 15 min after hysteroscopy.

Discussion

Hyskon is used by gynecologists as a distending medium for visualization during diagnostic and therapeutic hysteroscopy. At our institution, we had seen several cases of transient pulmonary edema with coagulopathy after the use of Hyskon for these purposes; one case required the patient's overnight stay in an intensive care unit (1). Several authors (1–5) have similarly reported pulmonary edema with Hyskon infusion volumes ranging from 300 to 1200 mL. Of the 42 cases of laser hysteroscopy that had been completed at our institution by 1988, Hyskon had been used in only 22 of them; however, it has been used in all of the most recent 16 cases. The mean dose ± standard deviation was 480 ± 236 mL. Pulmonary edema did not develop in any patient, but postoperative hypoxia requiring supplemental oxygen developed in one patient in whom 600 mL of Hyskon was used. Three others were given furosemide prophylactically to induce diuresis and to avoid fluid overload (1).

As the Hyskon level was arbitrarily set not to exceed 500 mL and as patients have been described to suffer intraoperative problems with Hyskon levels between 300 and 1200 mL (1–5), we tried to correlate the amount of Hyskon used with serum levels with evidence of coagulopathy, and with pulmonary edema. However, no pulmonary edema or coagulopathy developed.

We postulate that Hyskon is absorbed in a manner similar to the way fluids are absorbed during transurethral prostatectomy when the vascular bed is open to the irrigating fluid. However, during hysteroscopy, extremely high instillation pressures were used for irrigation, resulting in intravascular absorption and/or injection. As each patient's requirement for Hyskon varies depending on the size of the uterus and the extent of the operation, we noted a higher concentration of Hyskon in the patient's blood as more Hyskon was used at 15- and 30-min intervals. Figure 1 shows the statistically significant relationship between dose and serum Hyskon levels. This study is the first to document the entrance of Hyskon into the bloodstream. Cleary et al. (7) observed clinical ascites 2 days after intraperitoneal instillation of 250 mL of Hyskon, but no dextran was found in the serum for the first 24 h. Hence, in our patients, Hyskon was absorbed or injected into the bloodstream.

Dextran-40, a product of the biodegradation of Hyskon, may have side effects such as factitious elevations in blood glucose level, error in blood cross-matching, decreased platelet adhesiveness, renal failure, and decreased plasma levels of fibrinogen and of factors V, VIII, and IX (8), in addition to those caused by Hyskon itself.

In our patients who underwent ablative procedures that resulted in open vascular bed in combination with high injection pressures, serum levels in excess of 1000 mg% were seen 30 min after an amount of Hyskon greater than 300 mL was used. During ablation, these open vascular beds in the endometrium seem to facilitate Hyskon absorption directly by injection into the bloodstream as, in most cases, injection pressures were greater than or equal to 380 mm Hg, and intrauterine pressures were between 40 and 120 mm Hg. Unfortunately, we were unable to monitor both pressures simultaneously because of limited monitoring ports on the hysteroscope. Lukacsko (4) stated that volumes of Hyskon greater than 500 mL given intravenously may cause pulmonary edema secondary to increases in plasma volume. Because of the osmotic properties of Hyskon, every 100 mL of Hyskon is expected to expand plasma volume by 860 mL (3). Thus, when the serum level of our highest absorber (patient 11) was 2900 mg% (approximately 227 mL of Hyskon in the blood), the plasma volume would have been expanded by 1952 mL. If the amount of Hyskon used was doubled, the increase in volume would be 3904 mL, enough to induce pulmonary edema in a compromised patient (Table 3). Although the mechanism of pulmonary edema associated with some drugs, including methadone, heroin, propoxyphene, salicylates, and dextran-40 is unknown (9,10), the pulmonary edema associated with Hyskon would seem to indicate that the mechanism is purely secondary to fluid overload, based on the foregoing results.

In summary, we report findings of intrauterine Hyskon absorption and/or injection during hysteroscopy, even after volumes of Hyskon as small as 50–100 mL were used. The intravascular volume expansion that results from absorption of Hyskon may be greater than that seen during transurethral prostatectomy because of pressurized injection and hypertonicity of the medium. We observed that serum concentrations were lower in patients having diagnostic procedures than in patients with ablative procedures ($P < 0.01$). As we noted increased serum Hyskon levels with increased dose used, we recommend that the minimum necessary dose of Hyskon be used. Injection pressures should be as low as possible to minimize the amount of intravascular injection. In cases in which large ablative procedures are necessary, we suggest that a two-stage operation be considered.

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A Survey of 800 Patients' Knowledge, Attitudes, and Concerns Regarding Anesthesia

Ketan Shevde, MD, and Georgia Panagopoulos, PhD

Department of Anesthesia, Maimonides Medical Center, Brooklyn, New York

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The present study was undertaken to assess patients' knowledge, attitudes, and concerns regarding anesthetic management. A survey of 34 items was developed and administered preoperatively to 800 consecutive patients. Included were 303 men and 497 women with a mean age 52 yr and a mean educational level of 12 yr. Patients were interviewed on their knowledge of the role and training of anesthesiologists and on their preferences regarding anesthetic management. Patients also rated the intensity of their concern on 20 written statements expressing potential anesthetic complications. Results indicated that patients' perceptions of the anesthesiologist's training and role were accurate. Most patients preferred (a) general to regional anesthesia and (b) not to select their own anesthesiologist. Most significant preoperative concerns regarding the anesthesiologist focused on experience, qualifications, and presence or absence during the anesthesia. Patient concerns also included the possibility of not waking up postoperatively, experiencing pain, and becoming paralyzed. Intensity of concern was inversely related to age and unrelated to educational level or occupation. Variables related to type of concern included patient's sex, type of anesthesia, and proposed surgical procedure. Issues of least concern included disclosure of personal matters during anesthesia, experiencing impaired judgment postoperatively, and being asleep or bedridden for a prolonged period of time. It is suggested that anesthesiologists address significant patient concerns during the preoperative visit to enhance their effectiveness in patient care. Efforts to educate the public on the anesthesiologist's role in perioperative care should improve patient confidence.

(Anesth Analg 1991;73:190–8)

A good anesthesiologist-patient relationship established during the preoperative visit reduces patient anxiety (1–3). This can be achieved by informing patients about their anesthetic management and addressing their specific concerns regarding anesthesia. Although a personal interview with the patient decreases anesthesia-related anxiety, few efforts have been directed at identifying the patients' greatest concerns. Only one recent study has assessed, and that only peripherally, patients' preference for anesthetic procedures and their preoperative fears (4). Results of that survey indicated that the majority (93%) of the patients preferred general anesthesia induced by intravenous injection. A large number (40%) of patients feared either postoperative pain or surgical complications (25%). Anxiety regarding the anesthetic procedure centered primarily on (a) fear of not waking up again, (b) waking up during the operation, (c) being unconscious, and (d) disclosing personal matters.

The present study was conducted to assess patients' knowledge about anesthesiologists and anesthetic management as well as their specific concerns about anesthesia. This information is essential for an effective preoperative visit.

Methods

Patient Population

The study was approved by the hospital's human research committee. All patients scheduled for surgery were included in the study. Excluded were patients who refused to participate or were unable to answer questions because of poor medical condition or inability to understand English.

The study was based on responses to 34 questions designed to assess the patients' perceptions, fears, and concerns relating to anesthesia. The questions, with input from 19 staff anesthesiologists, included ones commonly asked during preoperative visits. The initial section of the survey, oral in nature, was

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Accepted for publication April 10, 1991.

Address correspondence to Dr. Shevde, Department of Anesthesia, Maimonides Medical Center, 4802 Tenth Avenue, Brooklyn, NY 11219.

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0003-2999/91/$3.50

administered by interviewers and included open-ended questions inquiring about patients' objective knowledge of the role and training of the anesthesiologist as well as their preferences regarding anesthetic procedures (i.e., "what is the role of the anesthesiologist?," "how many years of medical and residency training do you think your anesthesiologist has had?," "if you were to choose, what type of anesthesia would you prefer?," "would you like to choose your own anesthesiologist?"). Additionally, patients were questioned about their past surgical history and exposure to anesthetic procedures as well as whether they had been contacted by an anesthesiologist during this hospitalization. Finally, patients were asked the open-ended question "what are you most concerned about?" in an attempt to elicit their primary concerns with minimal prompting.

Subsequent to the completion of the oral part of the questionnaire, patients were presented with 20 written statements expressing concerns about potential complications associated with anesthesia. These included survey items 9 through 28 and are presented in the Appendix. Patients were asked to rate, on their own, the intensity of their concerns on a five-point Likert scale. A Likert scale is one in which the patient is asked to respond to written items in terms of degree of reaction. The ratings were as follows: 1 = not at all, 2 = somewhat, 3 = moderately, 4 = very much, 5 = extremely. For discretionary reasons, direct questions relating to death were purposely excluded to prevent undue patient anxiety. Finally, patients rated their confidence in the anesthesiologist and surgeon on the same scale and the relative importance of these two specialists as well as that of their medical doctor in their total perioperative care. The latter was rated on a 10-point scale ranging from 0 = not at all to 10 = extremely important. Patients required approximately 15 min to complete the questionnaire.

All patients scheduled for surgery were contacted by one of three trained interviewers within the 24 h before surgery. Ambulatory and hospitalized patients were included in the study. To safeguard against sensitizing the patients to potential anesthetic complications, interviewers remained present throughout the entire administration of the survey to reassure patients as needed.

Statistical Analyses

A coding guide for the survey items was developed to aid in the transcription of the survey data into a computer file. Accuracy of data entry was checked by examining the frequency of out-of-range coded responses on all survey items. This revealed a very low error frequency ranging from 0% to 0.4%. Statistical analyses were performed using BMDP (a biomedical statistical software package). Descriptive statistics (i.e., measures of central tendency, frequency distributions) were obtained on patients' demographics, knowledge of the role and training of the anesthesiologist, patient preferences regarding anesthetic management, and the type and intensity of their concerns. Patients' preferences for anesthetic procedures were coded as 1 = general, 2 = local, and 3 = spinal/epidural. We used the term "local anesthesia" to reflect both local infiltration and major peripheral nerve blocks, and "regional anesthesia" to reflect both local and spinal/epidural anesthesia. Correlational and χ^2-analyses were performed to examine the relationship between patient demographics (i.e., age, sex, educational level) and history variables (i.e., previous experience with anesthesia, having seen the anesthesiologist preoperatively, type of anticipated anesthesia and surgery) and patient concerns. Furthermore, patients' responses on the intensity of preoperative concerns were factor-analyzed using a principal factoring with iteration and orthogonal rotation. The factor analyses were run to determine whether specific factors/dimensions existed describing these concerns. Finally, independent-samples t-tests were used to evaluate the relative importance of the anesthesiologist compared with other medical specialists, as perceived by patients. A $P < 0.05$ was accepted as statistically significant.

Results

Patient Characteristics

Patient population consisted of 800 consecutive consenting adults undergoing elective major and minor surgery in a large metropolitan tertiary care hospital. Ambulatory patients comprised 30% of the total population. Subjects included 303 men and 497 women (mean age, 52 yr) with a mean educational level of 12 yr. Two percent of the patients refused to participate in the study. Although most patients answered all of the survey questions, the number of patients cited in the analyses may vary because of two factors: first, because of the addition of items on demographics and, second, because of missing data from incomplete surveys submitted by a few patients. Twenty-six percent of the patients were scheduled to undergo gynecologic procedures, 18% orthopedic, 15% genitourinary, 8% colorectal, 7% gastrointestinal, 3% open heart, and 23% various other procedures. Figures 1 and 2, as well as Table 1, present results on the ethnic and occupational backgrounds of the respondents.

Perceptions of the Anesthesiologist's Training and Role

Patients' perceptions of the medical school and residency training of anesthesiologists were, for the most part, accurate. Patients indicated that anesthesiologists

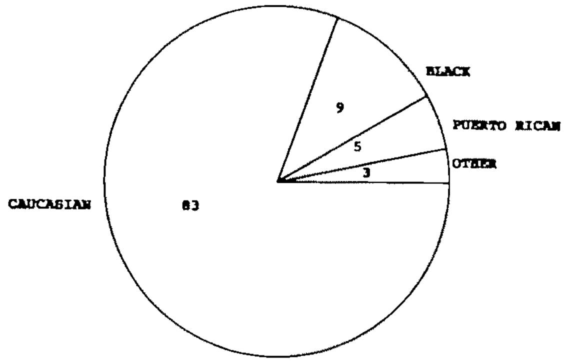

Figure 1. Demographic data ($n = 450$): ethnicity (%).

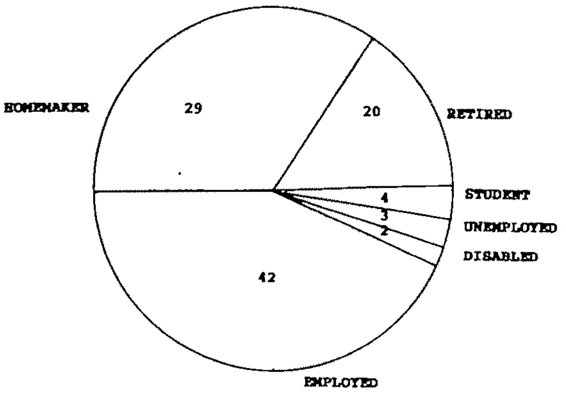

Figure 2. Demographic data ($n = 450$): employment status (%).

Table 1. Demographic Data ($n = 279$)[a]

Occupational level	Percent
Executive/professional	1
Business manager	3
Administrative personnel	21
Clerical/sales/technicians	42
Skilled manual	14
Semi-skilled	13
Unskilled	1
Other	5

[a] Reflects 62% of patients (42% employed and 20% retired).

spend a mean of 4.8 yr in medical school (SD = 1.4). Mean number of years spent in residency training was perceived to be 4.0 (SD = 1.9). Median and mode scores for each variable were 4.0. Figure 3 presents patients' perceptions of the anesthesiologist's role.

Overall, patients' ratings of their confidence in the anesthesiologist preoperatively fell into the "very high" level (mean, 3.97; SD, 1.07; range, 1–5). No significant differences were observed in confidence ratings of patients who had seen an anesthesiologist before providing a rating and those who had not seen one [t-test for independent samples (616) = 1.21, $P > 0.10$]. Confidence ascribed to the anesthesiologist, though very high, was significantly lower than that ascribed to the surgeon preoperatively (mean, 4.47; SD, 0.80; t-test (617) = −15.49; $P < 0.001$).

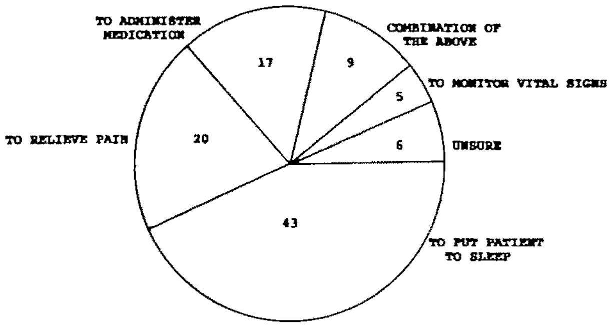

Figure 3. Perception of the anesthesiologist's role ($n = 800$): % patients.

Table 2. Ability to Choose the Anesthesiologist ($n = 800$)

Patient prefers to make a choice	% Patients	Reasons	%
Yes	23	Patient should control choice	17
		Patient needs recommendation	6
No	77	Patient does not know any	40
		Patient leaves decision to surgeon	14
		It does not matter	14
		Patient not qualified to	9

When patients were asked about the relative importance of the anesthesiologist, the surgeon, and the medical doctor in the total perioperative care, they rated the significance of the anesthesiologist as being at the same level as that of their medical doctor [t-test (522) = −1.61, $P = 0.10$]. Ratings of both specialists were significantly lower than those assigned to surgeons [t-test (527) = −5.52, $P < 0.001$ for the comparison between anesthesiologists and surgeons and t-test (527) = −5.62, $P < 0.001$ for medical doctors and surgeons].

Patients' Preferences for Anesthetic Management

The vast majority of patients (77%) were reluctant to select their own anesthesiologist primarily because they did not know any (40%), believed they were unqualified to do so (9%), or because it did not matter to them (14%). Fourteen percent of the patients believed that their surgeon would make that decision. Among the 23% of the patients who preferred to choose, 17% expressed a desire to have complete control of such a choice and 6% preferred to choose only if they knew an anesthesiologist or if one was recommended to them. These results are presented in Table 2.

Sixty-nine percent of the patients preferred to have general anesthesia so that they would not see/feel anything (66%) or because they believed spinal anes-

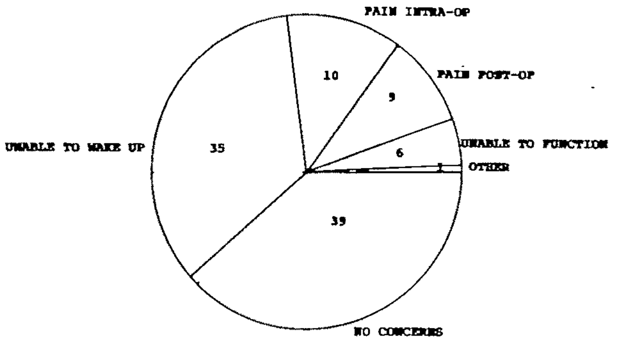

Figure 4. Fears/concerns expressed spontaneously by patients (n = 612): % patients.

thesia to be dangerous (3%). Twenty-two percent of the patients expressed a preference for local anesthesia because they wished to remain awake and aware throughout the procedure (13%) and to avoid side effects of general anesthesia (9%). Only 9% of the patients preferred either spinal or epidural anesthesia in order to remain awake and aware.

A 3×4 χ^2-analysis investigating whether type of anesthesia experienced in the past was related to current preferences revealed that patients tended to prefer the type of anesthesia they had had in the past. That is, more patients who had received general anesthesia preferred general and more patients who had received spinal anesthesia preferred spinal (χ^2-test (6) = 92.8, $P < 0.001$ [n = 547]). The number of patients who had had local anesthesia or combinations of types of anesthesia was too small to yield valid results.

Among the 254 first-time surgical patients, there was a strong preference for general anesthesia (72%), followed by local (22%) and spinal/epidural (6%) anesthesia. This finding mirrored the preferences of the total population.

Patients' Preoperative Concerns

Patients' concerns regarding anesthetic management were assessed in two ways: first, patients were asked the open-ended question "what are you most concerned about?" Their responses are presented in Figure 4.

Second, patients were asked to rate the degree of their concern on 20 written statements specific to being hospitalized and receiving anesthesia. Table 3 presents in a descending order the percentage of patients who assigned "very much" or "extremely" levels of concern to these areas of anesthetic management. These items were classified into three categories: issues of highest, moderate, and least concern.

Factor analysis of preoperative concerns yielded four factors: (a) specific complications of anesthesia, (b) characteristics of the anesthesiologist, (c) anxiety about being hospitalized, and (d) pain. Each of these factors was examined further to determine whether the variables loaded highly on the appropriate factor. Most of the variables did load on the appropriate factor as expected. Table 4 presents the items comprising each factor and item loadings. Based on these results the scores from each item were added together to form four additional variables describing the above-reported dimensions.

Table 3. Issues of Concern (n = 800)

	% Patients indicating highest levels of concern
Highest concern	
Anesthesiologist's qualifications	45
Experience of anesthesiologist	43
Being unable to wake-up postop	37
Postop pain	34
Anesthesiologist present in OR	32
Patient becoming paralyzed	32
Pain medications available	28
Moderate concern	
Fear of the unknown	25
Waking up in the middle of surgery	24
Nervous of hospital environment	22
Postop nausea	22
Anesthesiologist's manners	22
Staying in ICU	21
Least concern	
Being unconscious	19
Prolonged sleep postop	18
Being bedridden	16
Fear of needles	13
Impaired judgment	12
Clarity of thought	11
Disclosing personal matters	6

OR, operating room; ICU, intensive care unit.

Correlates of Patients' Preoperative Concerns

Patient demographics. Pearson product moment and rank order correlation coefficients were computed between the patient's age, educational and occupational level, and degree of concern expressed on the above areas of anesthetic management. Table 5 presents these results. Overall, age showed a statistically significant, but weak inverse relationship with concern. That is, older patients tended to have lower levels of concern. Patients' educational level and occupation were not significantly related to degree of concern.

A 2×4 χ^2-analysis was performed investigating the effects of sex on patients' responses to the question "what are you most concerned about?" Type of concern was dependent on the patient's sex. More women were concerned about not waking up postoperatively, whereas more men were concerned about experiencing intraoperative and postoperative pain [χ^2-test (3) = 18.98, $P < 0.001$]. There was no

Table 4. Factor Analyses of Patients' Preoperative Concerns

Factor	Item loading
Specific anesthesia complications (factor 1)	
Impairment in judgment	0.772
Clarity of thought	0.763
Prolonged sleep postop	0.756
Being bedridden	0.660
Being put unconscious	0.635
Becoming paralyzed	0.613
Staying in ICU	0.613
Being unable to wake up postop	0.581
Disclosure of personal matters	0.471
Postop nausea	0.463
Anesthesiologist's characteristics (factor 2)	
Anesthesiologist's qualifications	0.875
Anesthesiologist of experience	0.842
Anesthesiologist present in OR	0.772
Anesthesiologist's manners	0.634
Anxiety about hospitalization (factor 3)	
Nervous of hospital environment	0.831
Fear of unknown	0.813
Fear of needles	0.613
Pain (factor 4)	
Pain medications available	0.828
Postop pain	0.813
Waking in middle of surgery	0.436

ICU, intensive care unit; OR, operating room.

Table 5. Correlations Between Patient's Demographics and Intensity of Concern

	Age (n = 508)	Education (n = 5–8)	Rank (n = 261)
Highest concern			
Anesthesiologist's qualifications	−0.11	−0.02	−0.01
Experience of anesthesiologist	−0.09	−0.05	−0.01
Being unable to wake-up postop	−0.21[a]	−0.07	−0.06
Postop pain	−0.18[a]	−0.08	−0.06
Anesthesiologist present in OR	−0.07	−0.04	−0.08
Patient becoming paralyzed	−0.21[a]	−0.10	−0.02
Pain medications available	−0.07	−0.01	−0.02
Moderate concern			
Fear of the unknown	−0.12[a]	−0.11	−0.09
Waking up in middle of surgery	−0.21[a]	−0.01	−0.00
Nervous of hospital environment	−0.14[a]	0.01	0.00
Postop nausea	−0.19[a]	0.10	−0.03
Anesthesiologist's manners	−0.18[a]	−0.02	−0.04
Staying in ICU	−0.19[a]	0.09	−0.04
Least concern			
Being unconscious	−0.19[a]	0.16[a]	−0.12
Prolonged sleep postop	−0.14[a]	0.07	−0.08
Being bedridden	−0.12[a]	0.07	−0.16[a]
Fear of needles	−0.19[a]	0.04	−0.07
Impaired judgment	−0.09	0.09	−0.05
Clarity of thought	−0.11	0.05	−0.08
Disclosing personal matters	−0.21[a]	0.09	−0.06

OR, operating room; ICU, intensive care unit.
[a] $P < 0.01$.

Table 6. Preoperative Responses on Factors by Patient's Sex

	Male		Female		
Variables	Mean	SD	Mean	SD	t
Specific anesthesia complications	1.95	0.88	2.25	0.99	−4.35[a]
Anesthesiologist's characteristics	2.52	1.24	2.72	1.34	−2.12[b]
Anxiety about hospitalization	1.91	0.88	2.49	1.02	−8.08[a]
Pain	2.37	1.01	2.62	1.14	−3.13[c]

[a] $P \leq 0.001$.
[b] $P \leq 0.05$.
[c] $P \leq 0.01$.

difference between men and women on expressing "no concern."

Moreover, independent-samples t-test analyses on the four new factors were performed to determine whether there were any differences between men and women on the level of concern they expressed preoperatively. Overall, women tended to express significantly higher levels of concern on all four factors: specific anesthesia complications [t-test (796) = −4.35, $P <$ 0.001]; generalized hospital anxiety [t-test (797) = −8.08, $P < 0.001$]; the anesthesiologist's characteristics [t-test (795) = −2.12, $P < 0.03$]; and pain [t-test (796) = −3.13, $P < 0.01$]. Table 6 presents the means and standard deviations for these analyses.

Patient history variables. χ^2-Analyses were performed to investigate the effects of past experience with anesthesia, type of anesthesia experienced, preoperative contact by an anesthesiologist, and type of anesthesia and surgery expected on the four spontaneously expressed categories of concern. To hold down the increase in error rates due to multiple comparisons, a more stringent α-level of 0.01 was set.

Neither previous experience with nor type of past anesthesia appeared to be related to patients' concerns [χ^2-test (3) = 2.59, P= 0.46 and χ^2-test (9) = 8.47, P = 0.48, respectively]. As 61% of patients had seen their anesthesiologist before completing the survey, a 2×4 χ^2-analysis was performed to determine whether frequency of concerns was dependent on having seen an anesthesiologist preoperatively. The result was not statistically significant [χ^2-test (3) = 5.68, P = 0.13], indicating that the frequency of four types of responses (no concerns, unable to wake up, and experiencing pain intraoperatively and postoperatively) was not dependent on such preoperative contact.

Patients' responses, however, depended on the type of anesthesia (general, local, spinal/epidural) and the type of surgery (ambulatory vs inpatient) expected.

More patients expecting general anesthesia were concerned about not waking up postoperatively and fewer of them were concerned about experiencing pain intraoperatively and postoperatively [χ^2-test (6) = 39.86, $P < 0.001$]. The reverse was true for patients expecting local or spinal/epidural anesthesia; more of them were concerned about intraoperative and postoperative pain. Consistent with this, patients undergoing major/nonambulatory surgery expressed these concerns more frequently and were less likely to deny any concerns [χ^2-test (3) = 42.77, $P < 0.001$]. Ambulatory patients were concerned about postoperative pain more frequently than expected by chance.

Discussion

This study was conducted to gain insight into patients' perception of anesthesiologists and anesthetic management. The majority of patients perceived the anesthesiologist's education and training accurately. Although some of the primary functions of the anesthesiologist were described correctly to include putting the patient to sleep, relieving pain, and administering medication, only 5% of the patients were aware that the anesthesiologist plays an important role in monitoring vital signs and maintaining normal hemodynamics throughout the operation. It appears that some patients are not sure what the anesthesiologist's functions are once the induction of anesthesia is completed. Hence the perception that the anesthesiologist might not be in attendance throughout the operative procedure is prevalent.

It is interesting to note that most of the patients (69%) had a strong preference for general anesthesia instead of regional anesthesia, especially as the latter is on the increase nationally. Patients preferred general anesthesia whether they had received it in the past or not.

When questioned about their concerns, most patients spontaneously expressed fears of not waking up postoperatively and experiencing intraoperative or postoperative pain or some type of postoperative disability. Concerns about the anesthesiologist's qualifications, experience, and continual presence in the operating room were only expressed when patients were specifically asked to comment on them. We would have to assume that these were not of foremost importance to the patients. Direct questions on death were omitted from the questionnaire to avoid undue patient anxiety. Information on this issue was obtained indirectly in two ways. First, in examining the intensity of their concern in the survey item "being unable to wake up postoperatively" and, second, in the frequency of answers relating to inability to wake up provided spontaneously by the patients to the open-ended question "what are you most concerned about?" Finally, our observation of the patients' preference for general anesthesia and the frequency of concerns such as being unable to wake up postoperatively and experiencing pain were consistent with the results obtained in the study by Elsass et al. (4).

Previous experience with anesthesia and having been interviewed by an anesthesiologist preoperatively were not related to patients' spontaneously expressed concerns. Overall, patients anticipating major/nonambulatory surgery expressed more concerns than expected by chance. Ambulatory patients were primarily concerned about experiencing postoperative pain. Consistent with this, patients anticipating general anesthesia were more frequently concerned about not waking up, whereas patients anticipating regional anesthesia were more concerned about experiencing intraoperative and postoperative pain. Women were more concerned about not waking up postoperatively, whereas men were more concerned about experiencing pain. Women tended to report significantly higher levels of concern on all variables than men. This difference may be attributed to sex role socialization which emphasizes decreased fear expression in males. It may be suggested that the lower concern levels expressed by men could be an artifact of the assessment method used and that the use of a clinical interview with a trained psychologist might have resulted in men "accurately" reporting more concern. We contend that this is not so. Both questionnaires and clinical interviews are based on patients' self-report. Therefore, it is likely that the factors that influence men's self-report operate equally when they answer a questionnaire and during a clinical interview. Such an interview, however, can be designed to yield the "expert's" rating on the patient's level of concern, which may more accurately reflect "reality" because it is based on the patient's self-report as well as the expert's behavioral observations of the patient (5). Unfortunately, the size of our study made it prohibitive to have such interviews. Regarding our recommendations, as it remains unclear whether men were "truly" less concerned or just reported so, it seems important that the anesthesiologist be aware of this possibility and appropriately address indications of even low concern levels in men.

Despite the significance assigned to the anesthesiologist's qualifications, an overwhelming number of patients (77%) were reluctant to select their own anesthesiologist primarily because of their unfamiliarity with anesthesiologists and lack of ability to select an anesthesiologist. Fourteen percent of the patients left such a decision to the surgeon because they believed that the surgeon would make the best choice for them. Apparently, patients were unaware that the choice of the anesthesiologist does not always lie with the surgeon.

In addition to gaining knowledge by identifying the patient's fund of information, attitudes, and concerns regarding anesthetic management, the results of this study identify issues the anesthesiologist ought to focus on during the preoperative visit. We believe that the anesthesiologist should specifically address patients' concerns regarding waking up and experiencing pain and inform them about the anesthesiologist's role in monitoring vital signs and maintaining normal hemodynamics. It seems important to inform patients that the anesthesiologist is, in fact, the internist in the operating room.

Moreover, there seems to exist a need to educate the patients and the general public about the role of the anesthesiologist in the perioperative care of the patient. This may narrow the gap in the confidence levels that the patients ascribed to the surgeon relative to the anesthesiologist. Future efforts directed at improving our communication with patients and increasing our exposure in the community via newspaper reports and lectures should achieve higher levels of patient confidence in the anesthesiologist.

Appendix: Patient Survey

NAME: ________________________________ AGE: _____ SEX: ________

TYPE OF OPERATION: ____________________________ DATE: __________

TYPE OF ANESTHESIA REGIONAL _____ LOCAL _____ GENERAL _____ EDUCATION __________

We are interested in finding out your perceptions of and attitudes toward anesthesia and the role of the anesthesiologist. Please answer the following questions to the best of your ability.

1. What, in your opinion, is the role of the anesthesiologist?

____

____

1b) Are they doctors? _____ Yes _____ No

2. How many years of medical training do you think your anesthesiologist has had? Please circle one

Number of years of medical school education 1 2 3 4 5 6

Number of years of residency training 1 2 3 4 5 6

3. Have you had an operation requiring anesthesia in the past?

_______ Yes _______ No

4. Type of surgery ______________________

Date of surgery ______________________

5. Under what type of anesthesia did you have your surgery?

_______ General _______ Spinal _______ Local

6. If you were to choose, what type of anesthesia would you prefer?

_______ Spinal

_______ Epidural

_______ Local

_______ General (asleep and completely unconscious).

Why? ____

____

6b) If the anesthesiologist recommended a different type of anesthesia would you agree or disagree with him?

_____ Agree _____ Disagree

7. Would you like to choose your own anesthesiologist?

_______ Yes _______ No Why ______________________________

____

8. Have you seen your anesthesiologist yet?
_________ Yes _________ No
8b) What are you most concerned about?

____

____

____

Please indicate the extent to which you have thought about the following by circling the number that corresponds to your answer.

	Not at all	Somewhat	Moderately	Very much	Extremely
9. Feeling nervous in the hospital environment.	1	2	3	4	5
10. Being afraid of the unknown.	1	2	3	4	5
11. Being afraid of needles.	1	2	3	4	5
Are you concerned about:					
12. Letting yourself fall into an unconscious state.	1	2	3	4	5
13. Disclosing personal matters involuntarily while under anesthesia.	1	2	3	4	5
14. Waking up in the middle of the operation.	1	2	3	4	5
15. Feeling pain after the operation.	1	2	3	4	5
16. Not having medication in time to relieve your pain/discomfort.	1	2	3	4	5
17. Anesthesia affecting the clarity of your thoughts.	1	2	3	4	5
18. Anesthesia impairing your judgment.	1	2	3	4	5
19. Being asleep for a long time after the operation.	1	2	3	4	5
20. Being unable to get out of bed for a prolonged period of time as a result of the anesthesia.	1	2	3	4	5
21. Having to stay in the intensive care unit for a prolonged period of time.	1	2	3	4	5
22. Being nauseous after the operation.	1	2	3	4	5
23. Becoming paralyzed because of the anesthesia.	1	2	3	4	5
24. Being unable to wake up from the anesthesia.	1	2	3	4	5
25. Whether the anesthesiologist will have good bedside manners.	1	2	3	4	5
26. Whether the anesthesiologist will stay in the operating room with you throughout the operation.	1	2	3	4	5
27. Your anesthesiologist being fully qualified to give you anesthesia.	1	2	3	4	5
28. Your anesthesiologist not being experienced enough to handle your situation.	1	2	3	4	5

29. If you have any concerns did you mention them to anyone?
_____ Yes _____ No I mentioned them to: Anesthesiologist _____ Surgeon _____ Other doctor _____ Family _____ Other _____

30. Please rate your confidence in your anesthesiologist.	1	2	3	4	5
31. Please rate your confidence in your surgeon.	1	2	3	4	5

32. How important do you think your anesthesiologist is in your total perioperative care (care before, during, and after the surgical procedure)?

Please circle:
0 1 2 3 4 5 6 7 8 9 10
Not at all Extremely

33. How important do you think your surgeon is in your total perioperative care (care before, during, and after the surgical procedure)?

Please circle:
0 1 2 3 4 5 6 7 8 9 10
Not at all Extremely

34. How important do you think your medical doctor is in your total perioperative care (care before, during, and after the surgical procedure)?

Please circle:
0 1 2 3 4 5 6 7 8 9 10
Not at all Extremely

DEMOGRAPHIC INFORMATION

1. Which of the following best describes you?
   1. American Indian
   2. Caucasian/White
   3. Chicano
   4. Indian
   5. Negro/black
   6. Oriental
   7. Puerto Rican
   8. Other (please describe) ____________________

2. Religious background.
   1. Jewish
   2. Catholic
   3. Protestant
   4. None
   5. Other ____________

3. Occupation.
   A. What is your occupational status (circle all that apply):
      1. Homemaker
      2. Student
      3. Disabled
      4. Unemployed, looking for work
      5. Employed
   B. If you are employed, what is the title of your job and the type of work that you do?

   ____

   ____

The authors thank Susan Tuchler, MS, Betsy Beeber, RN, and Rashmi Trivedi, MD, for interviewing the patients and collecting the data; James DeVito, BA, for assisting with manuscript preparation; and Pat Celentano for preparing the graphics. We also thank Paul G. Barash, MD, for his review of the manuscript.

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L-644,711, a Novel Anion Transport Inhibitor, Increases Isoflurane MAC in Rats

Jerry S. Matsumura, MD, Daniel J. Cole, MD, Randall M. Schell, MD,
and Michael H. Wong, BS

Department of Anesthesiology, Loma Linda University, Loma Linda, California

The effect of the anion transport inhibitor L-644,711 on isoflurane MAC was determined in rats ($n=24$). After baseline MAC determination, each rat received one of the following drug protocols: (a) control, vehicle only; (b) L-644,711$_{IT}$, a 3-mg/kg intrathecal bolus of L-644,711 followed by an infusion at 1.5 mg·kg^{-1}·h^{-1}; or (c) L-644,711$_{IV}$, a 6-mg/kg intravenous bolus of L-644,711 followed by an infusion at 3 mg·kg^{-1}·h^{-1}. MAC was again determined. The baseline isoflurane MAC was not different between groups (control, 1.52% ± 0.15%; L-644,711$_{IT}$, 1.51% ± 0.24%; L-644,711$_{IV}$, 1.54% ± 0.13% [mean ± SD]). After drug or vehicle administration, isoflurane MAC was larger for the L-644,711$_{IT}$ group (2.25% ± 0.17%) versus the control (1.38% ± 0.13%) and L-644,711$_{IV}$ (1.39% ± 0.15%) groups ($P < 0.05$). These data are consistent with the hypothesis that isoflurane anesthesia is influenced by anion channels and that blocking these channels may reduce the pharmacodynamic potency of isoflurane.

(Anesth Analg 1991;73:199–203)

The mechanism(s) whereby inhaled anesthetics induce anesthesia has not been delineated. Several theories have emerged as to the molecular target site(s) of anesthetic action and the associated physicochemical processes that occur. One hypothesis proposes that the site of anesthetic action is at the lipid membrane and that anesthetics effect conformational changes of membrane proteins that alter ion channel transport (1–5). In support of this theory is the observation that inhaled anesthetics functionally alter chloride channels in postsynaptic membranes (6).

γ-Amino butyric acid (GABA), a major neurotransmitter in mammalian brain, mediates the function of inhibitory neurons by binding to a specific receptor protein in postsynaptic membranes. Inhaled anesthetics may increase GABA receptor binding, effecting an increase in chloride conductance with membrane hyperpolarization and synaptic inhibition (7). This premise is supported by studies that demonstrate an increase in GABA-mediated inhibition by volatile anesthetics, and the induction of general anesthesia by a GABA analogue (8,9).

Accordingly, if transmembrane chloride channels were functionally blocked, the anesthetic potency of volatile anesthetics might be affected. In this study, using the tail clamp method to determine MAC (10–12), we evaluated the effect of the anion transport inhibitor L-644,711 on isoflurane MAC in rats. L-644,711 is a prototype drug from the [(2,3,9,9a-tetrahydro-3-oxo-9a-substituted-1H-fluoren-7-yl)oxy]-alkanoic acid series of compounds that have been developed to inhibit edema after traumatic brain injury (13).

Methods

The study protocol was reviewed and approved by the Animal Research Committee of Loma Linda University in accordance with guidelines on animal care by the U.S. Department of Health and Human Services. All studies were performed beween 7 AM and 3 PM in male, Sprague-Dawley rats (Harlan Sprague-Dawley Co., Indianapolis, Ind.) of similar ages. Anesthesia was achieved with 2.0% isoflurane in an oxygen/air mixture at 1.0 L/min (fraction of inspired $O_2 \sim 0.40$) with spontaneous ventilation via a mask. Via the atlantooccipital membrane, a PE-10 catheter was placed in the subarachnoid space and secured in place (14). Bupivacaine (0.25%) was infiltrated into the wound. Each rat was allowed to emerge from anesthesia and normal neurologic function was verified.

After a 60-min recovery period, each rat was rean-

Accepted for publication April 10, 1991.

Address correspondence to Dr. Cole, Department of Anesthesiology, Loma Linda University, Loma Linda, CA 92354.

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0003-2999/91/$3.50

esthetized with isoflurane, orotracheally intubated (15), and mechanically ventilated with a Harvard Rodent Respirator (Harvard Co., Boston, Mass.) at a rate of 60 breaths/min and a tidal volume of 10 mL/kg. With the aid of a surgical microscope, the femoral vessels were cannulated for continuous blood pressure monitoring (Full Scale Transducer/TA 2000 Recorder; Gould, Cerritos, Calif.) and for drug and maintenance fluid (0.9% NaCl at 4 $mL{\cdot}kg^{-1}{\cdot}h^{-1}$) administration. In pilot studies, when animals recovered after cannulation of the femoral artery, the lower extremities functioned normally and responded to stimulation. Physiologic parameters (pH, partial arterial pressure of CO_2, partial arterial pressure of O_2, mean arterial pressure [MAP], hematocrit, and glucose) were monitored during MAC determination (IL-1306 pH Blood Gas Analyzer, Instrumentation Laboratory, Lexington, Mass.; YSI model 23-A Glucose Analyzer, Yellow Springs Instruments, Yellow Springs, Ohio; IEC MB Centrifuge Microhematocrit, DAMON/IEC Division; Needham Heights, Mass.). Rectal temperature was servo-controlled at 37°C. The initial isoflurane concentration (1.65%, end-tidal) was based on previous determinations of isoflurane MAC in the rat and was designed to be slightly above MAC (16,17). A 120-min anesthetic stabilization period was allowed (the initial 20 min was a preparatory period, whereas the rat was left undisturbed for the final 100 min). Sampling of end-tidal gases has been previously detailed (11) and was achieved by a Puritan-Bennett Datex Capnomac infrared anesthetic gas analyzer with a sampling rate of 60 mL/min (Puritan-Bennett Co., Helsinki, Finland).

Isoflurane equilibration was verified at the end of the 120-min stabilization period and after each anesthetic change (defined as four successive end-tidal samples at 5-min intervals that differed by <5%). Each rat was stimulated by applying a full-length hemostat (20 cm) at the base of the tail to the full ratchet position. The hemostat was continuously moved for 60 s (10), and the presence or absence of purposeful movement was assessed by an observer blinded to study protocol. Dependent on the rat's response, end-tidal isoflurane was adjusted by 0.20% and maintained for 20 min (equilibrium verified as defined above). This sequence was repeated until an isoflurane interval of 0.20% was bracketed by a positive and negative response. The midpoint of this interval was then tested (MAC defined as the end-tidal concentration of isoflurane midway between the highest concentration with a positive response and lowest concentration with a negative response).

Each rat was randomly assigned to one of the following groups based on L-644,711 administration (randomized before the first MAC) and after a 60-min equilibration period a second MAC was determined:

Control ($n = 8$)—vehicle only (a 20-μL bolus followed by an infusion at 10 μL/h),

L-644,711$_{IT}$ (L_{IT}, $n = 8$)—an intrathecal bolus (3 mg/kg) and infusion (1.5 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$),

L-644,711$_{IV}$ (L_{IV}, $n = 8$)—an intravenous bolus (6 mg/kg) and infusion (3 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$).

The intrathecal dose of L-644,711 was based on pilot studies in which a bolus of 3 mg/kg and infusion at 1.5 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ consistently produced a shift in the electroencephalogram (EEG) from burst suppression to an α-wave pattern. (Higher doses effected a spike-and-wave pattern on the EEG, whereas lower doses did not consistently change the EEG.) The intravenous dose was based on pilot studies in which doses greater than a bolus of 6 mg/kg and infusion at 3 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ produced changes in the EEG. An analysis of the blood-to-brain pharmacokinetics would predict a much larger serum concentration of L-644,711 in the L_{IV} group versus the L_{IT} group. All groups had an equal volume of carrier solution given intrathecally and intravenously.

The data were compared by an analysis of variance and, as appropriate, *t*-tests with a Bonferroni correction factor were performed (18). A *P* value of <0.05 was considered significant. All data are reported as mean ± SD.

Results

Except for MAP, there were no significant differences between groups in the physiologic data (Table 1). There were no between-group differences in the isoflurane requirement to achieve MAC before intrathecal vehicle, intrathecal L-644,711, or intravenous L-644,711 administration. The isoflurane MAC was ~63% greater for the group that received intrathecal L-644,711 than for the group that received intravenous L-644,711 or vehicle only (*P*<0.05, Table 2).

Discussion

The results of this study demonstrate that when L-644,711 was delivered to the central nervous system, and presumably transmembrane chloride channels were blocked, the anesthetic potency of isoflurane was affected (MAC increased by ~63%). These data support the hypothesis that ion channels are a mediator of isoflurane anesthesia. This study does not establish that L-644,711 reverses isoflurane anesthesia, only that isoflurane MAC is greater after intrathecal L-644,711. The possible reversal of isoflurane anesthesia by L-644,711 is a matter of speculation and can only be addressed with additional stud-

Table 1. Physiologic Data at the Baseline (No Drug or Vehicle) and Second (After Drug or Vehicle) MAC Determinations

	Control	L-644,711$_{IT}$	L-644,711$_{IV}$
Baseline MAC			
Age (days)	229 ± 12	232 ± 15	237 ± 13
Weight (g)	476 ± 20	471 ± 33	486 ± 29
pH (U)	7.41 ± 0.04	7.41 ± 0.04	7.42 ± 0.04
Pao$_2$ (mm Hg)	140 ± 30	153 ± 25	150 ± 35
Paco$_2$ (mm Hg)	37.5 ± 3.1	37.4 ± 2.4	38.2 ± 3.0
Hematocrit (%)	45 ± 1	46 ± 1	46 ± 1
MAP (mm Hg)	93 ± 15	88 ± 8	89 ± 11
Glucose (mg/dL)	133 ± 22	142 ± 18	127 ± 17
Second MAC			
pH (U)	7.40 ± 0.02	7.39 ± 0.03	7.41 ± 0.02
Pao$_2$ (mm Hg)	131 ± 29	136 ± 22	145 ± 37
Paco$_2$ (mm Hg)	39.1 ± 3.8	37.9 ± 3.1	37.9 ± 2.9
Hematocrit (%)	45 ± 2	46 ± 1	46 ± 1
MAP (mm Hg)	92 ± 13[a]	135 ± 11[a]	112 ± 13[a]
Glucose (mg/dl)	127 ± 24	130 ± 16	120 ± 17

Paco$_2$, partial arterial pressure of CO$_2$; Pao$_2$, partial arterial pressure of O$_2$; MAP, mean arterial pressure.

Control is the group in which the vehicle only was administered; L-644,711$_{IT}$, the group that received L-644,711 via the intrathecal route; and L-644,711$_{IV}$, the group that received L-644,711 via the intravenous route.

Data are mean ± SD.

[a] $P < 0.05$ between all three groups.

Table 2. Requirement of Isoflurane (% End-Tidal) to Achieve a 1.0 MAC Level of Anesthesia in Each of the Three Groups of Rats Before (First MAC) and After (Second MAC) Drug or Vehicle Administration

	Control	L-644,711$_{IT}$	L-644,711$_{IV}$
First MAC	1.52 ± 0.15	1.51 ± 0.24	1.54 ± 0.13
Second MAC	1.38 ± 0.13	2.25 ± 0.17[a]	1.39 ± 0.15

Control is the group in which the vehicle only was administered; L-644,711$_{IT}$, the group that received L-644,711 via the intrathecal route; and L-644,711$_{IV}$, the group that received L-644,711 via the intravenous route.

[a] $P < 0.05$ versus the control and L-644,711$_{IV}$ groups.

ies on the molecular interaction of L-644,711 and isoflurane anesthesia at anion channels.

L-644,711 is a [5,6-dichloro-(2,3,9,9a-tetrahydro-3-oxo-9a-(CH$_2$)$_2$CH$_3$-1H-fluoren-7-yl)oxy]alkanoic acid with a molecular weight of 369, a pKa of 3.6 (in 30% ethanol), and a nonsignificant salidiuretic activity (13). It has been well established that in brain L-644,711 completely inhibits the Cl$^-$/HCO$_3$$^-$ exchange system, with negligible effects on the Na$^+$ + K$^+$ + 2Cl$^-$ cotransport system (13,19). Although its molecular weight is low, L-644,711 has an extremely low penetrance of the blood-brain barrier under normal conditions (13). (L-644,711 is not detectable in cat brain after intravenous administration of ^{14}C-labeled L-644,711 [5 mg/kg].) However, any L-644,711 that does cross the blood-brain barrier has high intrinsic activity (although rat brain is less sensitive by ninefold compared with cat brain [13]). We know of no reports of side effects from the acute use of L-644,711, or nonspecific effects other than the inhibition of glutamate uptake into the neuron (glutamate antagonism) (19). As there is a significant interactive dependency of glutamate uptake into the neuron and chloride channels (20), it is difficult to discern the degree to which isoflurane potency was affected by a separate contribution by the glutamate antagonism property of L-644,711.

Explanations for the differences in MAC might include a methodologic bias, physiologic or pharmacokinetic factors, or nonspecific neurophysiologic/neurotransmitter aberrations. During the 120-min equilibration period each animal received 1.65% end-tidal isoflurane, which is 5%–10% above MAC for Sprague-Dawley rats (16,17), but much less than that necessary to prevent purposeful movement in the L$_{IT}$ group. Accordingly, about two extra tail clampings were needed to define MAC in the L$_{IT}$ group. Each tail clamping results in some tail trauma, which could cause neural damage and decrease transmission of noxious stimuli. The extra tail clampings also increased the duration of the study by approximately 40 min in the L$_{IT}$ group. We have not previously noted an effect of time or two extra tail clampings on MAC (17). However, a slight deterioration in MAC with time was observed in this study. This may have been a real effect of time, an influence of the intrathecal infusion, or some other unknown factor. If anything, this bias should have resulted in an underestimation of the real MAC value of isoflurane after intrathecal L-644,711. Further methodologic biases were minimized by randomization, comparison with appropriate control groups, an all-or-none criterion to define MAC, and the use of an observer blinded to anesthetic constituents and drug treatment. The protocol of the present study would tend to be validated by previous studies of isoflurane MAC in Sprague-Dawley rats (MAC=1.57% and 1.58%) (16,17).

The only physiologic variable that was significantly different between groups was MAP. Although extreme degrees of hypotension have been shown to affect MAC (10,21), the influence of hypertension is not obvious. Most of the evidence suggests hypertension does not affect MAC provided there are no concurrent changes in neurotransmitter activity (10,22–27). At least two possible mechanisms may account for this elevation in MAP. First, L-644,711 may directly increase MAC, resulting in a lighter plane of anesthesia and a subsequent catecholamine release with an increase in MAP. Second, L-644,711 may directly activate the sympathetic nervous system with an elevation in central catecholamines, which might increase MAC (and MAP). There are no data to support either of these hypotheses, and further study is needed to more clearly delineate the relative possibilities of these mechanisms.

A critique of this study is the ability of L-644,711 to access the intrathecal space. L-644,711 has a low penetrance of the blood-brain barrier (28). Accordingly, it became necessary to deliver L-644,711 to the brain by some other means than intravenously. Using the intrathecal catheterization technique described in this manuscript, we demonstrated that intrathecal L-644,711 reduced the area of focal cerebral ischemic injury in rats (29). In addition, intrathecal placement was confirmed at necropsy by injecting 3% Evans Blue through the catheter. Accordingly, the intrathecal catheter probably provided a means of effectively accessing brain tissue with L-644,711. However, data on the anatomic distribution of this drug in the brain would be valuable and could be obtained by a radionucleotide study. Other pharmacokinetic variables were controlled by defining MAC within a narrow interval, rigidly defining limits of anesthetic equilibrium, and carefully sampling the end-tidal gases.

One of the mechanisms whereby isoflurane is proposed to produce anesthesia is by increasing GABA receptor binding, which increases transmembrane chloride conductance, resulting in membrane hyperpolarization and synaptic inhibition (7–9). The results of this study support this hypothesis (i.e., isoflurane is proposed to increase GABA receptor binding, which increases transmembrane chloride conductance; with this drug we inhibited transmembrane chloride conductance and consequently "antagonized" the interactive effect of isoflurane and GABA on chloride channels). This hypothesis is further supported by pilot studies on the EEG effects of intrathecal L-644,711. In rats given a low dose of intrathecal L-644,711, the EEG pattern shifted from burst suppression (1.2 MAC isoflurane [1.87%, end-tidal]) to activation and arousal. At higher doses of intrathecal L-644,711, spike wave activity was evident on the EEG without clinical evidence of seizure activity.

In conclusion, the isoflurane requirement to achieve MAC was ~63% greater in rats that received intrathecal L-644,711 than in the group that received vehicle only or intravenous L-644,711 ($P < 0.05$, see Table 2). These data support the hypothesis that isoflurane anesthesia is mediated via anion channels. Blocking these channels may effect a neurophysiologic condition in which isoflurane is pharmacodynamically less efficacious. Further studies are necessary before conclusions regarding a precise mechanism of this apparent anesthetic *antagonism* of isoflurane by L-644,711 can be made.

The authors gratefully acknowledge the technical assistance of Terrill Osborne and Suzzanne Marcantonio. The authors also acknowledge the assistance of H.K. Kimelberg, PhD, and James Kohut in obtaining L-644,711 powder from Merck Sharp and Dohme Research Laboratories.

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Effects of Dexmedetomidine, a Novel Imidazole Sedative-Anesthetic Agent, on Adrenal Steroidogenesis: In Vivo and In Vitro Studies

Mervyn Maze, MB, ChB, Raimo Virtanen, PhD, David Daunt, DVM, Stephen J.M. Banks, BS, E. Price Stover, MD, and David Feldman, MD

Departments of Anesthesia, Medicine, and Cellular and Molecular Physiology, Stanford University School of Medicine, Stanford, California; Anesthesiology Service, VAH, Palo Alto, California; and Orion Corporation, FARMOS, Turku, Finland

Inhibition of steroidogenesis may be produced perioperatively by imidazole compounds, such as the hypnotic agent etomidate, with potentially serious consequences for patient morbidity and mortality. Dexmedetomidine, ({+}4-[1-{2,3-dimethylphenyl}-ethyl]-1H-imidazole), another imidazole compound with anestheticlike properties, is now being used perioperatively. Therefore, we investigated the effects of dexmedetomidine on steroidogenesis as well as on binding to glucocorticoid receptors in a series of in vitro and in vivo animal studies. The effect of dexmedetomidine, 10^{-8}–10^{-3} M, on adrenocorticotrophic hormone (ACTH) stimulated release of corticosterone was assessed in isolated rat adrenal cells. To characterize dexmedetomidine interactions with the glucocorticoid receptor, dexmedetomidine's ability to compete for [^{3}H]dexmethasone binding sites was studied in renal tubular cells. The effect of dexmedetomidine, 80 μg/kg subcutaneously, on ACTH-stimulated release of cortisol was studied in separate cohorts of dogs at various time intervals during and after anesthesia was given. To compare the inhibitory effects of etomidate and dexmedetomidine on steroidogenesis, ACTH-stimulated release of cortisol was studied in dogs treated with anesthetic doses of either dexmedetomidine (80 μg/kg IV) or etomidate (1 mg/kg IV). Finally, dogs were given dexmedetomidine by continuous subcutaneous infusion for 7 days at sedative doses after which their cortisol response to ACTH was determined. At dexmedetomidine concentrations greater than 10^{-7} M, a dose-dependent inhibition of corticosterone release was detected in response to ACTH stimulation in vitro. At these high dexmedetomidine concentrations, [^{3}H]dexamethasone binding was not affected. In the in vivo dog experiments, basal cortisol levels decreased and the cortisol response to ACTH was blunted 3 h after dexmedetomidine administration. Continuously administered dexmedetomidine did result in decreased cortisol response to ACTH stimulation but was less than that observed after a single equianesthetic dose of etomidate. The authors conclude that dexmedetomidine inhibits steroid biosynthesis only in high concentrations. In the concentrations designed to provide either acute anesthesia or chronic sedation, dexmedetomidine does not cause the potent inhibitory effect on steroidogenesis seen after etomidate use. As this imidazole α_2-adrenergic agonist is highly efficacious as a sedative/hypnotic agent in the low nanomolar range, an important biologic effect on steroidogenesis probably will not occur clinically.

(Anesth Analg 1991;73:204–8)

Imidazole compounds, including the short-acting sedative/hypnotic/anesthetic induction agent etomidate, inhibit steroidogenesis (1,2). Suppression of cortisol synthesis and hence glucocorticoid function was the suggested mechanism for the increased mortality rate seen in patients chronically sedated with etomidate in an intensive care setting (3,4). Subsequently, Wagner and White (5) established that surgical patients anesthetized with a single dose of etomidate (0.4 mg/kg) exhibited a diminished response to adrenocorticotrophic hormone (ACTH) when compared with a group of patients who received thiopental.

Dexmedetomidine, the pharmacologically active *d*-stereoisomer of the highly selective α_2-adrenergic agonist medetomidine (6), has potent anesthetic qual-

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Presented in part at the International Pharmacology Congress, July 1990 in Amsterdam, The Netherlands.

Accepted for publication March 15, 1991.

Address correspondence to Dr. Maze, Anesthesiology Service (112A), V.A. Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304.

ities (7) and is now being used clinically (8). Because dexmedetomidine is also an imidazole compound ({+}4-[1-{2,3-dimethylphenyl}ethyl]-1H-imidazole), we sought to investigate its effects on steroidogenesis. As antifungal imidazole compounds, such as ketoconazole, in addition to inhibiting steroidogenesis, also compete for glucocorticoid receptors and exhibit antagonist activity in the target cells (9), we also investigated the effects of dexmedetomidine on [^{3}H]dexamethasone binding to glucocorticoid receptors.

Methods

The protocol for these studies was approved by the Stanford Panel on Laboratory Animal Care and the Animal Care and Use Committee at the Palo Alto V.A. Medical Center.

Corticosterone Production by Rat Adrenocortical Cells: In Vitro

Isolated adrenal cells were prepared by collagenase digestion of adrenal glands freshly removed from male rats as previously described (10). Cells were preincubated with study drugs including dexmedetomidine, its levo rotatory enantiomer (MPV-1441), etomidate, and ketoconazole and then exposed to synthetic ACTH (Cortrosyn). Preliminary studies showed that 10 ng/mL of ACTH produced a greater than 15-fold rise in corticosterone (the rat glucocorticoid) production and was therefore the dose selected. Cells were incubated for an additional hour at 37°C in the presence of ACTH, after which they were removed by centrifugation and the cumulative corticosterone production was assessed by measuring the corticosterone concentration in the medium. Corticosterone was assayed by a radioimmunoassay technique (Endocrine Sciences, Oxnard, Calif.). The cells were shown to be viable as multiple washings of the cells always resulted in the successful restoration of corticosterone response back to normal.

Binding to Glucocorticoid Receptors: In Vitro

Kidneys were harvested and homogenized at 0°C in a medium containing 250 mM sucrose, 1.5 mM ethylenediaminetetraacetic acid, 10 mM Tris and 12 mM monothioglycerol, and 10 mM sodium molybdate, pH 7.8. Cytosol was prepared by centrifugation at 204,000 *g* for 30 min. Glucocorticoid receptor binding was assayed by incubating aliquots of cytosol with [^{3}H]dexamethasone (26 Ci/mmol, Amersham Corp., Arlington Heights, Ill.) with or without competitors for 3 h at 0°C. Nonspecific binding was determined in the presence of a 250-fold excess of unlabeled dexamethasone. Bound hormone was separated from free hormone using minicolumns made with G-50 fine Sephadex (Pharmacia, Piscataway, N.J.) as previously described (9,10).

Acute Administration of Drugs to Dogs: In Vivo

On separate occasions, beagle dogs of either sex (9–13 kg) were given saline solution or hypnotic doses of either etomidate (1 mg/kg IV) or dexmedetomidine (80 μg/kg IM), and after 30 min blood was sampled for cortisol (the dog glucocorticoid) before and 60 min after intramuscular administration of 0.25 mg of ACTH. To define the time-course of dexmedetomidine's effect on steroidogenesis, 5 or 6 mongrel dogs weighing 15–20 kg were given a hypnotic dose of dexmedetomidine (80 μg/kg) or an equal volume of saline solution subcutaneously, and after a set time interval (see above) blood was sampled from a foreleg vein and plasma basal cortisol levels were measured. Synthetic ACTH (0.25 mg IM) was then administered, and 60 min later blood was sampled again for cortisol. In separate experiments, each dog (except where indicated) underwent a similar ACTH-stimulation test 0.5, 1, 3, 6, 12, and 24 h after dexmedetomidine administration.

Chronic Administration of Drugs to Dogs: In Vivo

Beagle dogs of both sexes weighing 9–14 kg were implanted with osmotic minipumps (Alzet, model 2ML2; Alza Corp., Palo Alto, Calif.) set to deliver either 3 or 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ or a like volume of saline solution (4.7 μL/h) subcutaneously. Seven days after implantation, an ACTH-stimulation test was performed. For both the acute and chronic in vivo experiments, plasma cortisol was assayed by the radioimmunoassay technique. For experiments in which beagles were used, the samples were assayed with the ^{125}I-cortisol RIA kit (Farmos Diagnostica, Turku, Finland), whereas for the mongrel dog experiments, the [^{3}H]cortisol RIA kit (ICN-Biomedical) was used.

Statistics

A two-way repeated measures analysis of variance was used for statistical analysis in which treatment was the grouping factor and time the within factor.

Results

Corticosterone Production by Rat Adrenocortical Cells: In Vitro

Dexmedetomidine displayed a dose-dependent inhibition of ACTH-stimulated corticosterone production

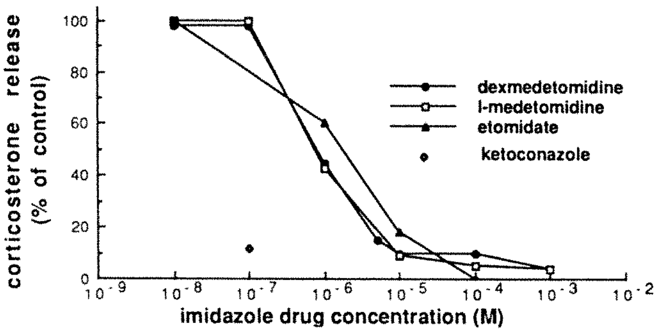

Figure 1. Effect of imidazole compounds on cumulative corticosterone production in response to ACTH stimulation in isolated rat adrenocortical cells. Cell dispersions were preincubated with the following substituted imidazoles: etomidate, dexmedetomidine, or L-medetomidine. ACTH (10 ng/mL) was added and cells were incubated for an additional hour after which the medium was sampled for corticosterone by radioimmunoassay.

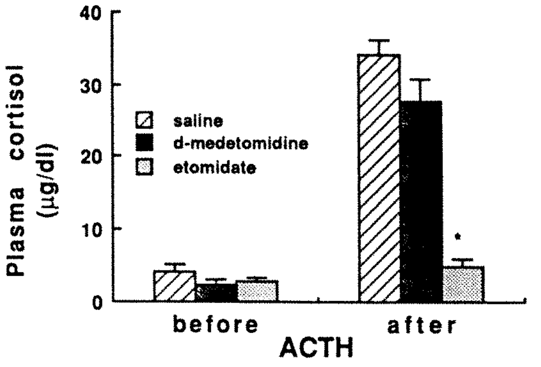

Figure 2. Comparative effects of dexmedetomidine or etomidate on ACTH-stimulated plasma cortisol in beagle dogs. Anesthesia was induced with dexmedetomidine (80 μg/kg) (n = 6) or etomidate (1 mg/kg) (n =4) and 30 min later baseline plasma samples were obtained (*before*). ACTH (0.25 mg/kg IM) was administered and 60 min later plasma was sampled for cortisol by radioimmunoassay (*after*). Control animals (n = 11) received saline solution. A two-way repeated measures analysis of variance was used for statistical analysis in which treatment was the grouping factor and time was the within factor. $^*P < 0.05$ from the control values. Data are represented as mean ± SEM.

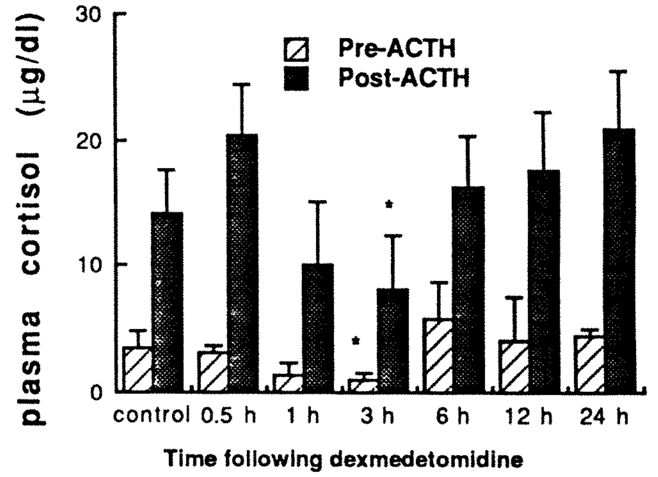

Figure 3. Effect of dexmedetomidine on ACTH-stimulated plasma cortisol in mongrel dogs. Dogs were given intramuscularly a hypnotic dose of dexmedetomidine (80 μg/kg) or saline solution (control, n = 5). At set time intervals [0.5 (n = 5), 1 (n = 5), 3 (n = 6), 6 (n = 6), 12 (n = 5), and 24 (n = 5) h] after dexmedetomidine administration (in separate experiments), blood was sampled for plasma cortisol (*Pre*). Sixty minutes after ACTH administration (0.25 mg IM), blood was sampled again for cortisol (*Post*). A two-way repeated measures analysis of variance was used for statistical analysis in which treatment was the grouping factor and time was the within factor. $^*P < 0.05$ from the control values. Data are represented as mean ± SD.

with an IC_{50} of 10^{-6} M whereas the IC_{50} for etomidate was 2 × 10^{-6} M (Figure 1). By comparison, 10^{-8} M, ketoconazole totally blocked ACTH-stimulated corticosterone production (Figure 1). MPV-1441, the levo rotatory enantiomer of dexmedetomidine which lacks anesthetic activity (11), was as efficacious as the anesthetically active D isomer in blocking ACTH-stimulated corticosterone production, suggesting that the imidazole structure and not the anesthetic potency led to inhibition of steroidogenesis.

Binding to Glucocorticoid Receptors: In Vitro

[^{3}H]Dexamethasone binding to kidney cytosol was used in an assay for glucocorticoid receptor binding. Whereas unlabeled dexamethasone competed for 50% of the receptors labeled by 13 nM [^{3}H]dexamethasone at a molar ratio of ~threefold, dexmedetomidine, even at a molar ratio of greater than 10^4:1, failed to compete for dexamethasone binding sites. By comparison, ketoconazole potently competes for glucocorticoid receptors, reducing [^{3}H]dexamethasone binding by 50% at 2 × 10^{-5} M, a molar ratio of ~100:1 (data not shown).

Acute Studies: In Vivo

In the beagle dog group (Figure 2), the control animals showed a substantially greater ACTH-stimulated response than the control mongrel dogs (Figure 3). The ACTH response in the beagles went from 4.1 to 34.2 μg/dL of cortisol, which represents an eightfold increase (Figure 2). In the beagles that received dexmedetomidine, cortisol increased from 2.2 to 27.5 μg/dL or 12-fold. Thus, the incremental change 30 min after dexmedetomidine administration was 25 μg/dL compared with 30 μg/dL in the control group. The etomidate-treated group went from a plasma cortisol value of 2.7 to 4.8 μg/dL, less than a twofold increase, confirming the potent inhibitory effect of etomidate on ACTH-stimulated cortisol (2,5).

The baseline and ACTH-stimulated cortisol levels

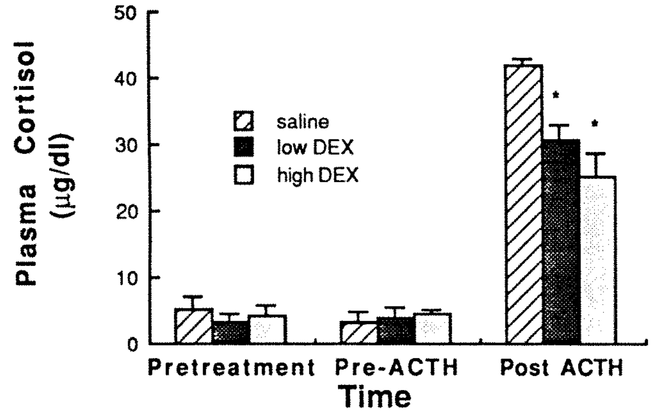

Figure 4. Effects of dexmedetomidine infusion on ACTH-stimulated plasma cortisol in beagle dogs. Osmotic pumps were inserted subcutaneously in beagles to infuse dexmedetomidine at rates of either 3 (low DEX, $n = 4$) or 10 mg·kg^{-1}·h^{-1} (high DEX, $n = 4$) for 7 days. Control animals received the saline solution alone ($n = 5$). Plasma cortisol levels were drawn three times: before siting the infusion pump (pretreatment), after 7 days of infusion (pre-ACTH), and 60 min after ACTH (post-ACTH). A two-way repeated measures analysis of variance was used for statistical analysis in which treatment was the grouping factor and time was the within factor. *$P < 0.05$ from the control values. Data are represented as mean ± SEM.

in mongrel dogs are shown at 0.5, 1, 3, 6, 12, and 24 h after intramuscular administration of 80 µg/kg of dexmedetomidine or saline solution (Figure 3). Compared with the saline-treated animals, the basal values of cortisol significantly decreased 3 h after dexmedetomidine administration, at which time the animals were deeply anesthetized. After ACTH stimulation, there was at least a threefold rise in plasma cortisol at all times; once again at 3 h, the absolute post-ACTH plasma cortisol levels were significantly less than in the saline-treated animals.

The quantitative differences noted in the ACTH-stimulation tests of the control cohorts for these two series of in vivo experiments may be explained by the different breeds of dogs used (12).

Chronic Studies

Using Alzet minipumps, three groups of beagle dogs received either saline solution or low doses or high doses of dexmedetomidine at a rate of 3 or 10 µg·kg^{-1}·h^{-1}, respectively. These doses were chosen to produce sedation without obvious anesthesia. As shown in Figure 4, similar basal cortisol levels were noted before and after a 7-day infusion. There was a 12-fold increase in plasma cortisol after ACTH stimulation in the saline-infused beagles compared with an eightfold and sixfold rise in the low- and high-dose dexmedetomidine-infused beagles, respectively. A dose-dependent inhibition of ACTH-stimulated cortisol production was therefore demonstrated in the chronic dexmedetomidine-treated beagles.

Discussion

Dexmedetomidine, in concentrations above 10^{-7} M, produced a dose-dependent inhibition of corticosterone release in response to ACTH stimulation (Figure 1). [^{3}H]Dexamethasone binding to glucocorticoid receptors was not inhibited by dexmedetomidine, even at the highest concentration tested. Administration of a single high dose of dexmedetomidine to mongrel dogs inhibited adrenocortical function at 3 h after administration (Figure 3). This inhibition was manifested by a slight decrease in basal cortisol and by a decrement in the ACTH-stimulated cortisol. In beagle dogs tested 30 min after dexmedetomidine was given, a slight decrease was noted (Figure 2). However, this single time point may have missed the peak inhibitory effect on steroidogenesis (~3 h). In contrast, an anesthetic dose of etomidate profoundly inhibits the ACTH stimulation test (Figure 2). The blunting of steroidogenesis after dexmedetomidine administration does not coincide precisely with the anesthetic response as no significant attenuation is seen at 30 min, at which time the animals are deeply anesthetized. Continuous subcutaneous infusion of dexmedetomidine for 7 days at relatively high doses (3 and 10 µg^{-1}·kg^{-1}·h^{-1}) slightly suppressed the response to ACTH stimulation (Figure 4).

These studies, performed independently in two laboratories, qualitatively demonstrated the same findings, i.e., that high doses of dexmedetomidine are capable of inhibiting steroidogenesis. However, dexmedetomidine is not as potent as etomidate at inhibiting steroidogenesis. Although the precise anesthetic equivalent doses of etomidate and dexmedetomidine have not been established in the dog, preliminary human studies indicate these to be in the order of 100:1, etomidate/dexmedetomidine (13). As the molecular weights of these compounds are similar, biologically important inhibition of steroidogenesis is not likely to follow the acute anesthetic administration of dexmedetomidine. Although blunting of steroidogenesis was noted after both acute and chronic administration of dexmedetomidine (Figure 4), inhibition of steroidogenesis was much lower than could be produced after a single dose of etomidate (Figure 2).

Imidazole compounds such as etomidate have a well-documented effect on steroidogenesis (1,2,5, 10,14). At low concentrations these compounds inhibit 11 β-hydroxylase, whereas at higher concentrations, the cholesterol side-chain cleavage enzyme activity is also inhibited. Both of these are mitochondrial cytochrome P450 enzymes. Dexmedetomidine inhibits P450 microsomal drug metabolism in vitro but again only in the micromolar range (Pelkonen O et al., personal communication). Antipyrine elimination was only affected when doses in excess of 1000 μg/kg were used in vivo. Dexmedetomidine also inhibits alfentanil metabolism in the micromolar range (15). As noted, the inhibitory effect of dexmedetomidine on steroidogenesis is temporally out of phase with the peak hypnotic action (10). A possible reason for this discrepancy is that the dexmedetomidine concentrations may peak later in the adrenal cortex than in the brain.

The current studies are internally consistent with other work involving P450 enzyme-mediated processes and are illustrative of the low potency of dexmedetomidine for inhibiting P450 enzyme function compared with its anesthetic properties. Thus, there is some decrease in adrenal reserve but major ACTH responsiveness remains intact. If these studies can be extrapolated to the clinical anesthesia setting, then it is unlikely that a biologic effect on steroidogenesis will be noted in patients receiving dexmedetomidine as part of their anesthetic regimen. However, it will be important to investigate both the inhibition of steroid synthetic pathways in humans and the extent to which acutely and especially chronically administered dexmedetomidine in humans interferes with the metabolism of coadministered anesthetic drugs that require the involvement of P450 enzyme function.

This work was supported in part by the National Institutes of Health (GM 30232), the Veterans Administration, and Farmos Research. Dexmedetomidine and L-medetomidine were kindly supplied by Dr. Risto Lammintausta.

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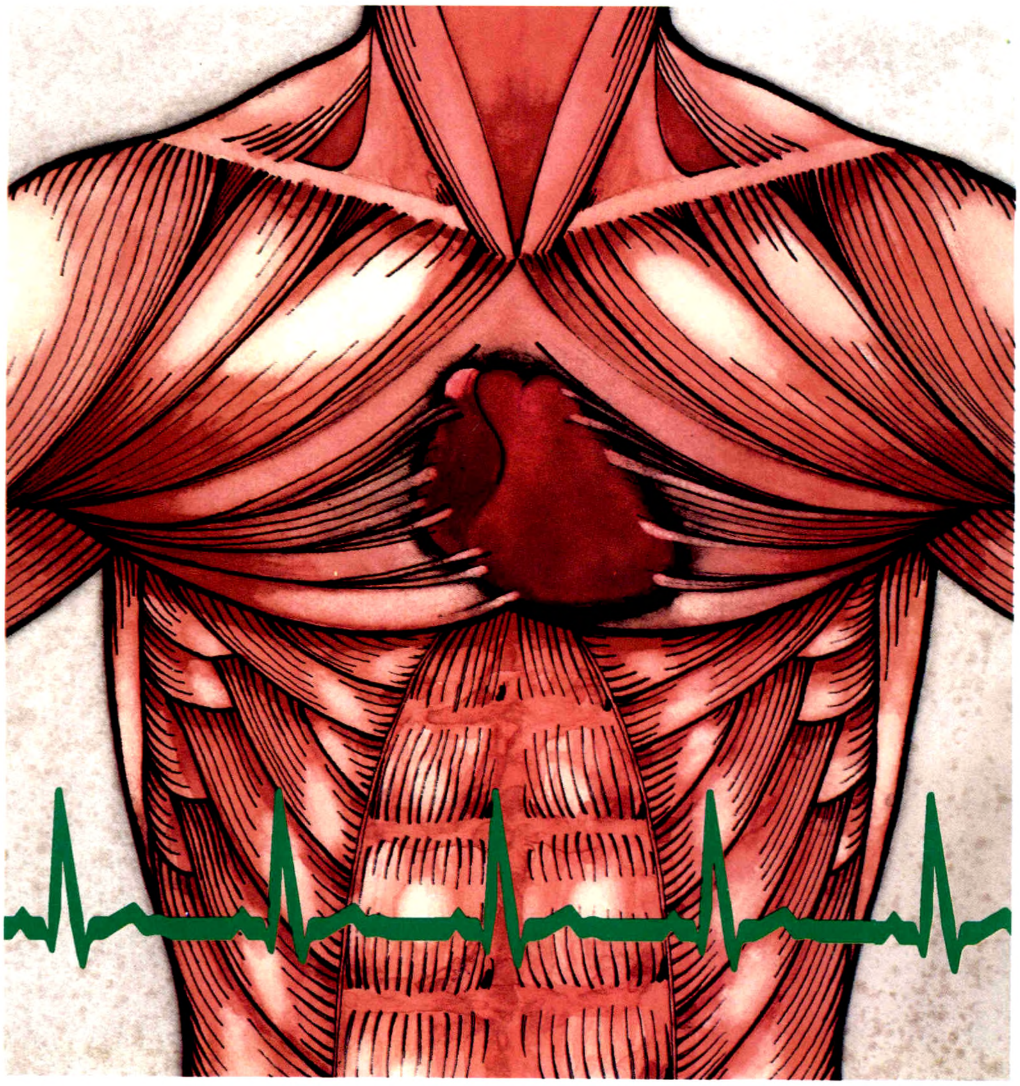

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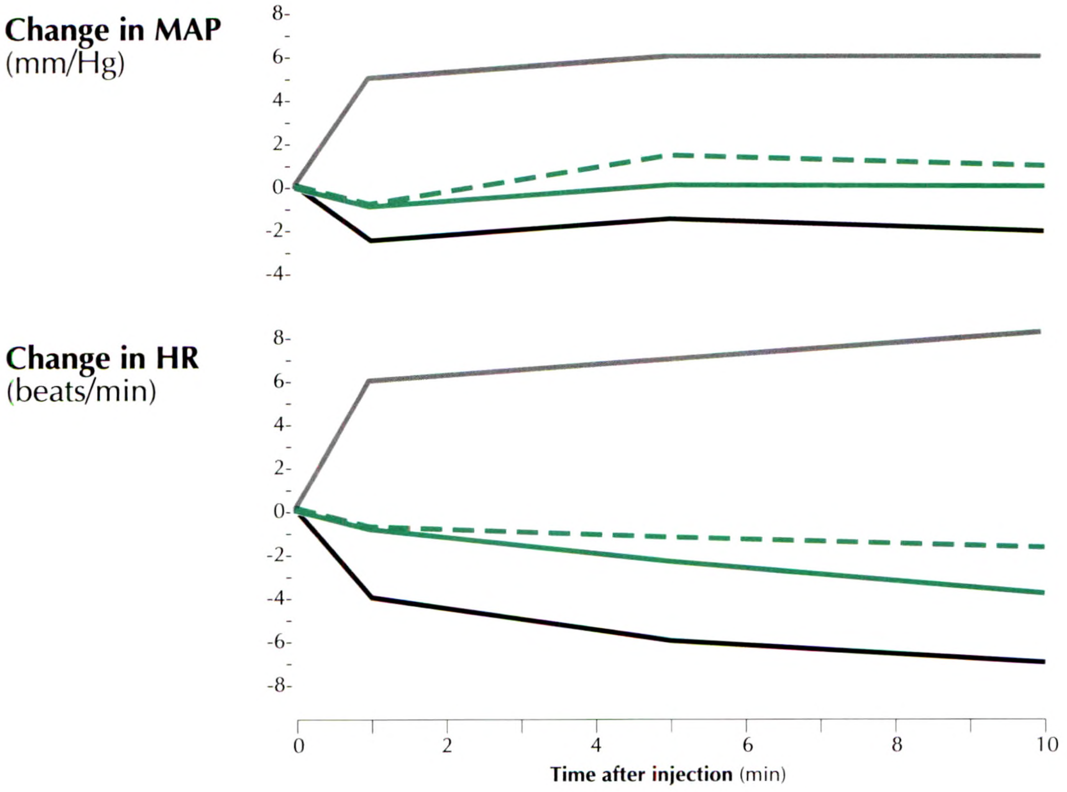
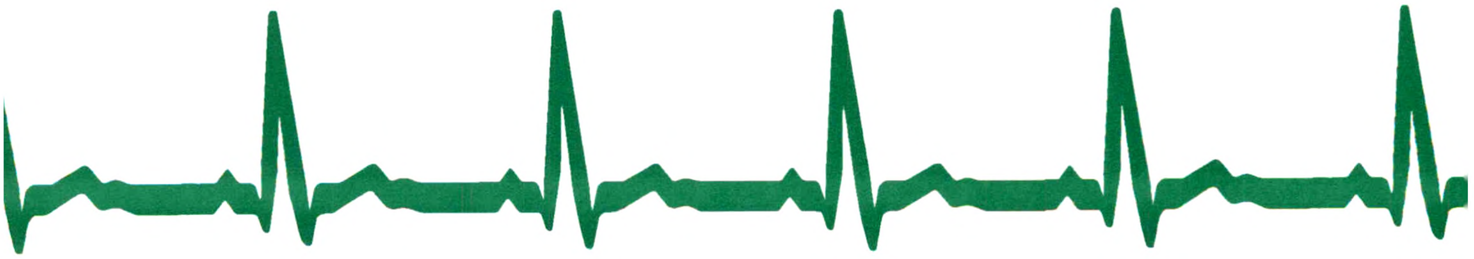


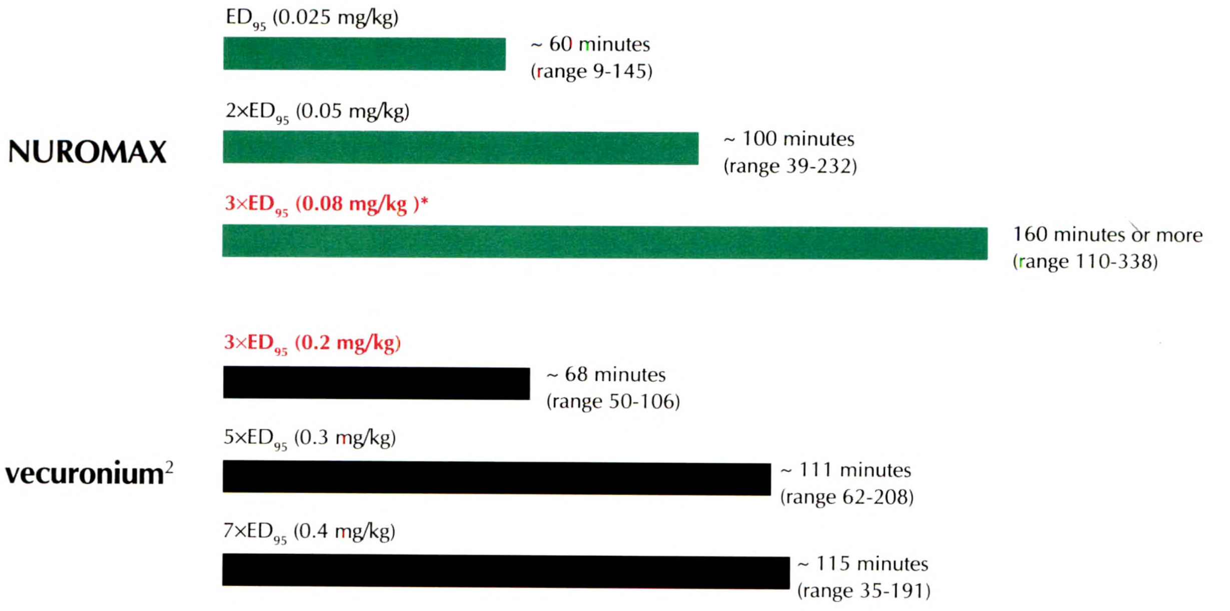
Emmott et al[1] compared the hemodynamic effects of Nuromax 0.037 and 0.075 mg/kg with the effects of pancuronium 0.09 mg/kg and vecuronium 0.075mg/kg in 36 CABG patients (9 patients, each group).
Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration.
All routine cardiac and vasoactive medications were continued up to the morning of surgery.

▬ ▬	doxacurium 0.037 mg/kg	▬	pancuronium 0.09 mg/kg
▬	doxacurium 0.075 mg/kg	▬	vecuronium 0.075 mg/kg



Longer acting than "high-dose" vecuronium

Clinically effective block (time to 25% recovery)



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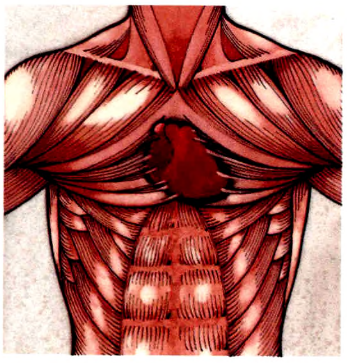
*This dose should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated.

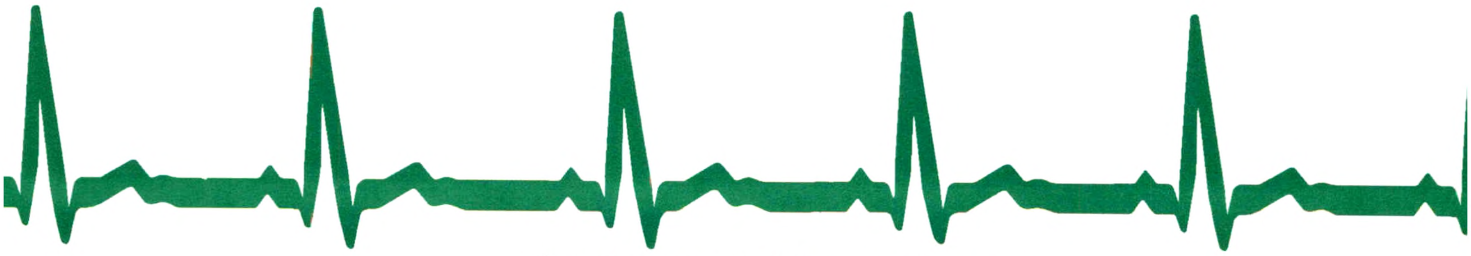
- **Cardiovascular stability comparable with normal saline** [3]
- **Noncumulative**
- **Ready-to-use solution**
- **Vials stored at room temperature, no refrigeration required**
- **Supplied as a 5 mL vial, 1 mg/mL**



NUROMAX® INJECTION

(doxacurium chloride) 1 mg/mL

Excellent for Long CV Procedures



Please see full prescribing information on following pages.

NUROMAX® INJECTION
(DOXACURIUM CHLORIDE)

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Nuromax (doxacurium chloride) is a long-acting, nondepolarizing skeletal muscle relaxant for intravenous administration. Doxacurium chloride is *trans, trans*-2,2'-[succinylbis(oxytrimethylene)]bis[1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride. The molecular formula is $C_{56}H_{78}Cl_2N_2O_{16}$ and the molecular weight is 1106.14. The compound does not partition into the 1-octanol phase of a distilled water/1-octanol system, *i.e.*, the n-octanol:water partition coefficient is 0.

Doxacurium chloride is a mixture of three *trans, trans* stereoisomers, a *dl* pair [(1*R*, 1'*R*, 2*S*, 2'*S*) and (1*S*, 1'*S*, 2*R*, 2'*R*)] and a meso form (1*R*, 1'*S*, 2*S*, 2'*R*).

Nuromax Injection is a sterile, non-pyrogenic aqueous solution (pH 3.9 to 5.0) containing doxacurium chloride equivalent to 1 mg/mL doxacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. Nuromax Injection contains 0.9% w/v benzyl alcohol.

CLINICAL PHARMACOLOGY: Nuromax binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.

Pharmacodynamics: Nuromax is approximately 2.5 to 3 times more potent than pancuronium and 10 to 12 times more potent than metocurine. Nuromax in doses of 1.5 to 2 x ED_{95} has a clinical duration of action (range and variability) similar to that of equipotent doses of pancuronium and metocurine (historic data and limited comparison). The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of Nuromax is 0.025 mg/kg (range: 0.020 to 0.033) in adults receiving balanced anesthesia.

The onset and clinically effective duration (time from injection to 25% recovery) of Nuromax administered alone or after succinylcholine during stable balanced anesthesia are shown in Table 1.

TABLE 1

Pharmacodynamic Dose Response[*] Balanced Anesthesia

	Initial Nuromax Dose (mg/kg)		
	0.025[†] (n=34)	0.05 (n=27)	0.08 (n=9)
Time to Maximum Block (min)	9.3 (5.4-16)	5.2 (2.5-13)	3.5 (2.4-5)
Clinical Duration (min) (Time to 25% Recovery)	55 (9-145)	100 (39-232)	160 (110-338)

[*] Values shown are means (range).

[†] Nuromax administered after 10% to 100% recovery from an intubating dose of succinylcholine.

Initial doses of 0.05 mg/kg (2 x ED_{95}) and 0.08 mg/kg (3 x ED_{95}) Nuromax administered during the induction of thiopental-narcotic anesthesia produced good-to-excellent conditions for tracheal intubation in 5 minutes (13 of 15 cases studied) and 4 minutes (8 of 9 cases studied) (which are before maximum block), respectively.

As with other long-acting agents, the clinical duration of neuromuscular block associated with Nuromax shows considerable interpatient variability. An analysis of 390 cases in U.S. clinical trials utilizing a variety of premedications, varying lengths of surgery, and various anesthetic agents, indicates that approximately two-thirds of the patients had clinical durations within 30 minutes of the duration predicted by dose (based on mg/kg actual body weight). Patients ≥ 60 years old are approximately twice as likely to experience prolonged clinical duration (30 minutes longer than predicted) than patients < 60 years old; thus, care should be used in older patients when prolonged recovery is undesirable (see **Geriatric Use** subsection of PRECAUTIONS and **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). In addition, obese patients (patients weighing ≥ 30% more than ideal body weight for height) were almost twice as likely to experience prolonged clinical duration than non-obese patients; therefore, dosing should be based on ideal body weight (IBW) for obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

The mean time for spontaneous T_1 recovery from 25% to 50% of control following initial doses of Nuromax is approximately 26 minutes (range: 7 to 104, n=253) during balanced anesthesia. The mean time for spontaneous T_1 recovery from 25% to 75% is 54 minutes (range: 14 to 184, n=184).

Most patients receiving Nuromax in clinical trials required pharmacologic reversal prior to full spontaneous recovery from neuromuscular block (see **Antagonism of Neuromuscular Block** subsection of OVERDOSAGE); therefore, relatively few data are available on the time from injection to 95% spontaneous recovery of the twitch response. As with other long-acting neuromuscular blocking agents, Nuromax may be associated with prolonged times to full spontaneous recovery. Following an initial dose of 0.025 mg/kg Nuromax, some patients may require as long as 4 hours to exhibit full spontaneous recovery.

Cumulative neuromuscular blocking effects are not associated with repeated administration of maintenance doses of Nuromax at 25% T_1 recovery. As with initial doses, however, the duration of action following maintenance doses of Nuromax may vary considerably among patients.

The Nuromax ED_{95} for children 2 to 12 years of age receiving halothane anesthesia is approximately 0.03 mg/kg. Children require higher Nuromax doses on a mg/kg basis than adults to achieve comparable levels of block. The onset time and duration of block are shorter in children than adults. During halothane anesthesia, doses of 0.03 mg/kg and 0.05 mg/kg Nuromax produce maximum block in approximately 7 and 4 minutes, respectively. The duration of clinically effective block is approximately 30 minutes after an initial dose of 0.03 mg/kg and approximately 45 minutes after 0.05 mg/kg. Nuromax has not been studied in children below the age of 2 years.

The neuromuscular block produced by Nuromax may be antagonized by anticholinesterase agents. As with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at reversal, the longer the time and the greater the dose of anticholinesterase required for recovery of neuromuscular function.

Hemodynamics: Administration of Nuromax doses up to and including 0.08 mg/kg (~3 x ED_{95}) over 5 to 15 seconds to healthy adult patients during stable state balanced anesthesia and to patients with serious cardiovascular disease undergoing coronary artery bypass grafting, cardiac valvular repair, or vascular repair produced no dose-related effects on mean arterial blood pressure (MAP) or heart rate (HR).

No dose-related changes in MAP and HR were observed following administration of up to 0.05 mg/kg Nuromax over 5 to 15 seconds in 2- to 12-year-old children receiving halothane anesthesia.

Doses of 0.03 to 0.08 mg/kg (1.2 to 3 x ED_{95}) were not associated with dose-dependent changes in mean plasma histamine concentration. Clinical experience with more than 1,000 patients indicates that adverse experiences typically associated with histamine release (*e.g.*, bronchospasm, hypotension, tachycardia, cutaneous flushing, urticaria, *etc.*) are very rare following the administration of Nuromax (see ADVERSE REACTIONS).

Pharmacokinetics: Pharmacokinetic and pharmacodynamic results from a study of 24 healthy young adult patients and 8 healthy elderly patients are summarized in Table 2. The pharmacokinetics are linear over the dosage range tested (*i.e.*, plasma concentrations are approximately proportional to dose). The pharmacokinetics of Nuromax are similar in healthy young adult and elderly patients. Some healthy elderly patients tend to be more sensitive to the neuromuscular blocking effects of Nuromax than healthy young adult patients receiving the same dose. The time to maximum block is longer in elderly patients than in young adult patients (11.2 minutes versus 7.7 minutes at 0.025 mg/kg Nuromax). In addition, the clinically effective durations of block are more variable and tend to be longer in healthy elderly patients than in healthy young adult patients receiving the same dose.

TABLE 2

Pharmacokinetic and Pharmacodynamic Parameters[1] of Nuromax in Young Adult and Elderly Patients

(Isoflurane Anesthesia)

Parameter	Healthy Young Adult Patients (22 to 49 yrs)			Healthy Elderly Patients (67 to 72 yrs)
	0.025 mg/kg (n=8)	0.05 mg/kg (n=8)	0.08 mg/kg (n=8)	0.025 mg/kg (n=8)
$t_{1/2}$ elimination (min)	86 (25-171)	123 (61-163)	98 (47-163)	96 (50-114)
Volume of Distribution at Steady State (L/kg)	0.15 (0.10-0.21)	0.24 (0.13-0.30)	0.22 (0.16-0.33)	0.22 (0.14-0.40)
Plasma Clearance (mL/min/kg)	2.22 (1.02-3.95)	2.62 (1.21-5.70)	2.53 (1.88-3.38)	2.47 (1.58-3.60)
Maximum Block (%)	97 (88-100)	100 (100-100)	100 (100-100)	96 (90-100)
Clinically Effective Duration of Block[2] (min)	68 (35-90)	91 (47-132)	177 (74-268)	97 (36-179)

[1] Values shown are means (range).

[2] Time from injection to 25% recovery of the control twitch height.

Table 3 summarizes the pharmacokinetic and pharmacodynamic results from a study of 9 healthy young adult patients, 8 patients with end-stage kidney disease undergoing kidney transplantation, and 7 patients with end-stage liver disease undergoing liver transplantation. The results suggest that a longer $t_{1/2}$ can be expected in patients with end-stage kidney disease; in addition, these patients may be more sensitive to the neuromuscular blocking effects of Nuromax. The time to maximum block was slightly longer and the clinically effective duration of block was prolonged in patients with end-stage kidney disease.

TABLE 3

Pharmacokinetic and Pharmacodynamic Parameters[1] of Nuromax in Healthy Patients and in Patients Undergoing Kidney or Liver Transplantation

(Isoflurane Anesthesia)

Parameter	Healthy Young Adult Patients	Kidney Transplant Patients	Liver Transplant Patients
	0.015 mg/kg (n=9)	0.015 mg/kg (n=8)	0.015 mg/kg (n=7)
$t_{1/2}$ elimination (min)	99 (48-193)	221 (84-592)	115 (69-148)
Volume of Distribution at Steady State (L/kg)	0.22 (0.11-0.43)	0.27 (0.17-0.55)	0.29 (0.17-0.35)
Plasma Clearance (mL/min/kg)	2.66 (1.35-6.66)	1.23 (0.48-2.40)	2.30 (1.96-3.05)
Maximum Block (%)	86 (59-100)	98 (95-100)	70 (0-100)
Clinically Effective Duration of Block (min)	36 (19-80)	80 (29-133)	52 (20-91)

[1] Values shown are means (range).

No data are available from patients with liver disease not requiring transplantation. There are no significant alterations in the pharmacokinetics of Nuromax in liver transplant patients. Sensitivity to the neuromuscular blocking effects of Nuromax was highly variable in patients undergoing liver transplantation. Three of 7 patients developed ≤ 50% block, indicating that a reduced sensitivity to Nuromax may occur in such patients. In those patients who developed > 50% neuromuscular block, the time to maximum block and the clinically effective duration tended to be longer than in healthy young adult patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Consecutively administered maintenance doses of 0.005 mg/kg Nuromax, each given at 25% T_1 recovery following the preceding dose, do not result in a progressive increase in the plasma concentration of doxacurium or a progressive increase in the depth or duration of block produced by each dose.

Nuromax is not metabolized *in vitro* in fresh human plasma. Plasma protein binding of Nuromax is approximately 30% in human plasma.

In vivo data from humans suggest that Nuromax is not metabolized and that the major elimination pathway is excretion of unchanged drug in urine and bile. In studies of healthy adult patients, 24% to 38% of an administered dose was recovered as parent drug in urine over 6 to 12 hours after dosing. High bile concentrations of Nuromax (relative to plasma) have been found 35 to 90 minutes after administration. The overall extent of biliary excretion is unknown. The data derived from analysis of human urine and bile are consistent with data from *in vivo* studies in the rat, cat, and dog, which indicate that all of an administered dose of Nuromax is recovered as parent drug in the urine and bile of these species.

Individualization of Dosages: In elderly patients or patients who have impaired renal function, the potential for a prolongation of block may be reduced by decreasing the initial Nuromax dose and by titrating the dose to achieve the desired depth of block. In obese patients (patients weighing ≥ 30% more than ideal body weight for height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2

Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Dosage requirements for patients with severe liver disease are variable; some patients may require a higher than normal initial Nuromax dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged in such patients relative to patients with normal liver function.

As with pancuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity and/or shortened duration of block, must be considered when Nuromax is selected for use in patients receiving phenytoin or carbamazepine (see **Drug Interactions** subsection of PRECAUTIONS).

As with other nondepolarizing neuromuscular blocking agents, a reduction in dosage of Nuromax must be considered in cachectic or debilitated patients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or carcinomatosis, and in other patients in whom potentiation of neuromuscular block or difficulty with reversal is anticipated. Increased doses of Nuromax may be required in burn patients (see PRECAUTIONS).

INDICATIONS AND USAGE: Nuromax is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia, to provide skeletal muscle relaxation during surgery. Nuromax can also be used to provide skeletal muscle relaxation for endotracheal intubation.

CONTRAINDICATIONS: Nuromax is contraindicated in patients known to have hypersensitivity to it.

WARNINGS: NUROMAX SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS NUROMAX EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANTS, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM.

NUROMAX HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Nuromax Injection is acidic (pH 3.9 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Nuromax Injection contains benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. See **Pediatric Use** subsection of PRECAUTIONS.

PRECAUTIONS: General: Nuromax has no clinically significant effects on heart rate; therefore, Nuromax will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (*e.g.*, myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (*e.g.*, carcinomatosis), the use of a peripheral nerve stimulator and a small test dose of Nuromax is recommended to assess the level of neuromuscular block and to monitor dosage requirements. Shorter acting muscle relaxants than Nuromax may be more suitable for these patients.

Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns depending upon the time elapsed since the injury and the size of the burn. Nuromax has not been studied in patients with burns.

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Nuromax has not been studied in patients with asthma.

No data are available to support the use of Nuromax by intramuscular injection.

Renal and Hepatic Disease: Nuromax has been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing transplantation procedures (see CLINICAL PHARMACOLOGY). The possibility of prolonged neuromuscular block in patients undergoing renal transplantation and the possibility of a variable onset and duration of neuromuscular block in patients undergoing liver transplantation must be considered when Nuromax is used in such patients.

Obesity: Administration of Nuromax on the basis of actual body weight is associated with a prolonged duration of action in obese patients (patients weighing ≥ 30% more than ideal body weight for height) (see CLINICAL PHARMACOLOGY). Therefore, the dose of Nuromax should be based upon ideal body weight in obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-susceptible patients. Since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of Nuromax in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of Nuromax.

The use of Nuromax before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on concomitant use of Nuromax and other nondepolarizing neuromuscular blocking agents.

Isoflurane, enflurane and halothane decrease the ED_{50} of Nuromax by 30% to 45%. These agents may also prolong the clinically effective duration of action by up to 25%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Nuromax include certain antibiotics (*e.g.*, aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine.

As with some other nondepolarizing neuromuscular blocking agents, the time of onset of neuromuscular block induced by Nuromax is lengthened and the duration of block is shortened in patients receiving phenytoin or carbamazepine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Nuromax was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, in the mouse lymphoma assay, and in the human lymphocyte assay. In the *in vivo* rat bone marrow cytogenetic assay, statistically significant increases in the incidence of structural abnormalities, relative to vehicle controls, were observed in male rats dosed with 0.1 mg/kg (0.625 mg/m^2) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in female rats dosed with 0.2 mg/kg (1.25 mg/m^2) Nuromax and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female rats given 0.3 mg/kg (1.875 mg/m^2) Nuromax and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic assay was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is low.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Teratology testing in nonventilated, pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of Nuromax revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Nuromax in pregnant women. Because animal studies are not always predictive of human response and the doses used were subparalyzing, Nuromax should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of Nuromax during labor, vaginal delivery, or cesarean section has not been studied. It is not known whether Nuromax administered to the mother has immediate or delayed effects on the fetus. The duration of action of Nuromax exceeds the usual duration of operative obstetrics (cesarean section). Therefore, Nuromax is not recommended for use in patients undergoing C-section.

Nursing Mothers: It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following Nuromax administration to a nursing woman.

Pediatric Use: Nuromax has not been studied in children below the age of 2 years. See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age.

Geriatric Use: Nuromax has been used in elderly patients, including patients with significant cardiovascular disease. In elderly patients the onset of maximum block is slower and the duration of neuromuscular block produced by Nuromax is more variable and, in some cases, longer than in young adult patients (see **Pharmacodynamics** and **Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: The most frequent adverse effect of nondepolarizing blocking agents as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesia. This effect may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency and apnea which require manual or mechanical ventilation until recovery is judged to be clinically adequate (see OVERDOSAGE). Inadequate reversal of neuromuscular block from Nuromax is possible, as with all nondepolarizing agents. Prolonged neuromuscular block and inadequate reversal may lead to postoperative complications.

Observed in Clinical Trials: Adverse experiences were uncommon among the 1034 surgical patients and volunteers who received Nuromax and other drugs in U.S. clinical studies in the course of a wide variety of procedures conducted during balanced or inhalational anesthesia. The following adverse experiences were reported in patients administered Nuromax (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater than 1% - None

Incidence Less than 1% -

Cardiovascular[*]:	hypotension,[†] flushing,[†] ventricular fibrillation, myocardial infarction
Respiratory:	bronchospasm, wheezing
Dermatological:	urticaria, injection site reaction
Special Senses:	diplopia
Nonspecific:	difficult neuromuscular block reversal, prolonged drug effect, fever

[*] Reports of ventricular fibrillation (n=1) and myocardial infarction (n=1) were limited to ASA Class 3-4 patients undergoing cardiac surgery (n=142).

[†] 0.3% incidence. All other reactions unmarked were ≤ 0.1%.

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (*e.g.*, neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent (see **Antagonism of Neuromuscular Block**).

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCK. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED. T_4/T_1 SHOULD BE > ZERO BEFORE ANTAGONISM IS ATTEMPTED.

In an analysis of patients in whom antagonism of neuromuscular block was evaluated following administration of single doses of neostigmine averaging 0.06 mg/kg (range: 0.05 to 0.075) administered at approximately 25% T_1 spontaneous recovery during balanced anesthesia, 71% of patients exhibited $T_4/T_1 \geq 0.7$ before monitoring was discontinued. For these patients, the mean time to $T_4/T_1 \geq 0.7$ was 19 minutes (range: 7 to 55). As with other long-acting nondepolarizing neuromuscular blocking agents, the time for recovery of neuromuscular function following administration of neostigmine is dependent upon the level of residual neuromuscular block at the time of attempted reversal; longer recovery times than those cited above may be anticipated when neostigmine is administered at more profound levels of block (*i.e.*, at < 25% T_1 recovery).

Patients should be evaluated for adequate clinical evidence of antagonism, *e.g.*, 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of Nuromax on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., < 60% T_1 recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block. The use of pyridostigmine has not been studied.

DOSAGE AND ADMINISTRATION: NUROMAX SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

Nuromax, like other long-acting neuromuscular blocking agents, displays variability in the duration of its effect. The potential for a prolonged clinical duration of neuromuscular block must be considered when Nuromax is selected for administration. The dosage information provided below is intended as a guide only. Doses should be individualized (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include: advancing age, the presence of kidney or liver disease, or obesity (patients weighing ≥ 30% more than ideal body weight for height). The use of a peripheral nerve stimulator will permit the most advantageous use of Nuromax, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Adults: *Initial Doses:* When administered as a component of a thiopental/narcotic induction-intubation paradigm as well as for production of long-duration neuromuscular block during surgery, 0.05 mg/kg (2 x ED_{95}) Nuromax produces good-to-excellent conditions for tracheal intubation in 5 minutes in approximately 90% of patients. Lower doses of Nuromax may result in a longer time for development of satisfactory intubation conditions. Clinically effective neuromuscular block may be expected to last approximately 100 minutes on average (range: 39 to 232) following 0.05 mg/kg Nuromax administered to patients receiving balanced anesthesia.

An initial Nuromax dose of 0.08 mg/kg (3 x ED_{95}) should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated. In approximately 90% of patients, good-to-excellent intubation conditions may be expected in 4 minutes after this dose; however, clinically effective block may be expected to persist for as long as 160 minutes or more (range: 110 to 338) (see CLINICAL PHARMACOLOGY).

If Nuromax is administered during steady-state isoflurane, enflurane, or halothane anesthesia, reduction of the Nuromax dose by one-third should be considered.

When succinylcholine is administered to facilitate tracheal intubation in patients receiving balanced anesthesia, an initial dose of 0.025 mg/kg (ED_{95}) Nuromax provides about 60 minutes (range: 9 to 145) of clinically effective neuromuscular block for surgery. For a longer duration of action, a larger initial dose may be administered.

Maintenance Doses: Maintenance dosing will generally be required about 60 minutes after an initial dose of 0.025 mg/kg Nuromax or 100 minutes after an initial dose of 0.05 mg/kg Nuromax during balanced anesthesia. Repeated maintenance doses administered at 25% T_1 recovery may be expected to be required at relatively regular intervals in each patient. The interval may vary considerably between patients. Maintenance doses of 0.005 and 0.01 mg/kg Nuromax each provide an average 30 minutes (range: 9 to 57) and 45 minutes (range: 14 to 108), respectively, of additional clinically effective neuromuscular block. For shorter or longer desired durations, smaller or larger maintenance doses may be administered.

Children: When administered during halothane anesthesia, an initial dose of 0.03 mg/kg (ED_{95}) produces maximum neuromuscular block in about 7 minutes (range: 5 to 11) and clinically effective block for an average of 30 minutes (range: 12 to 54). Under halothane anesthesia, 0.05 mg/kg produces maximum block in about 4 minutes (range: 2 to 10) and clinically effective block for 45 minutes (range: 30 to 80). Maintenance doses are generally required more frequently in children than in adults. Because of the potentiating effect of halothane seen in adults, a higher dose of Nuromax may be required in children receiving balanced anesthesia than in children receiving halothane anesthesia to achieve a comparable onset and duration of neuromuscular block. Nuromax has not been studied in children below the age of 2 years.

Compatibility: *Y-site Administration:* Nuromax Injection may not be compatible with alkaline solutions with a pH greater than 8.5 (*e.g.*, barbiturate solutions).

Nuromax is compatible with:

- 5% Dextrose Injection USP
- 0.9% Sodium Chloride Injection USP
- 5% Dextrose and 0.9% Sodium Chloride Injection USP
- Lactated Ringer's Injection USP
- 5% Dextrose and Lactated Ringer's Injection
- Sufenta® (sufentanil citrate) Injection, diluted as directed
- Alfenta® (alfentanil hydrochloride) Injection, diluted as directed
- Sublimaze® (fentanyl citrate) Injection, diluted as directed

Dilution Stability: Nuromax diluted up to 1:10 in 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP has been shown to be physically and chemically stable when stored in polypropylene syringes at 5° to 25°C (41° to 77°F), for up to 24 hours. Since dilution diminishes the preservative effectiveness of benzyl alcohol, aseptic techniques should be used to prepare the diluted product. Immediate use of the diluted product is preferred, and any unused portion of diluted Nuromax should be discarded after 8 hours..

HOW SUPPLIED: Nuromax Injection, 1 mg doxacurium in each mL.

5 mL Multiple Dose vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS). Tray of 10 (NDC 0081-0763-44).

STORAGE: Store Nuromax Injection at room temperature of 15° to 25°C (59° to 77°F). DO NOT FREEZE.

U.S. Patent No. 4701460

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1. Emmott RS, Bracey BJ, Goldhill DR, Yate PM, Flynn PJ. Cardiovascular effects of doxacurium, pancuronium and vecuronium in anaesthetized patients presenting for coronary artery bypass surgery. *Br J Anaesth.* 1990;65:480-486.
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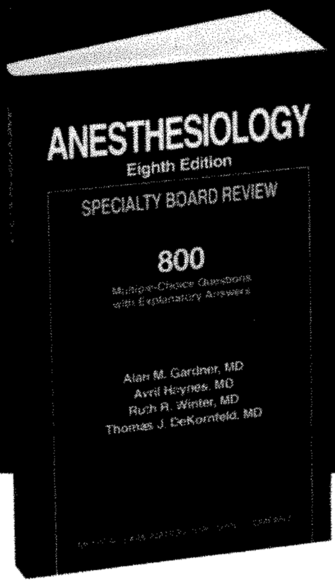

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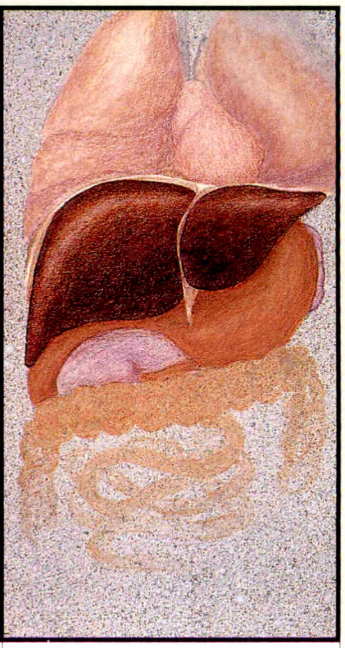
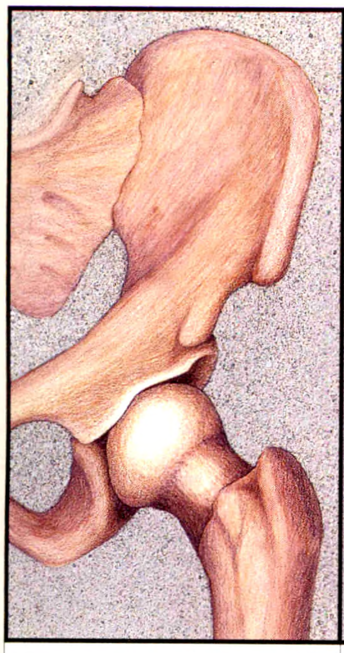
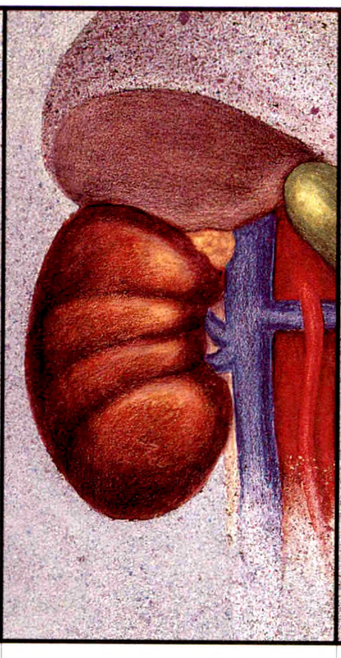
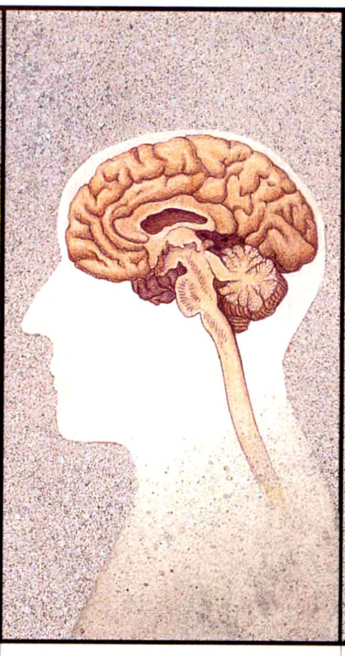
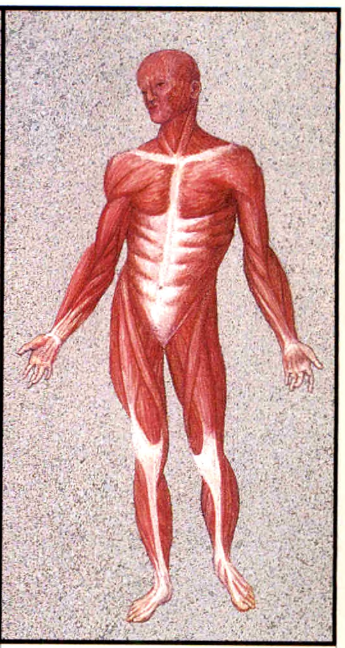


Cholecystectomy	Biliary tract repair
Common patient type Obese	**Common patient type** Both adults and children
Advantage of Tracrium No difference in recovery from neuromuscular blockade between normal and obese patients. Recovery time with vecuronium can take three times as long in the obese patient.[1]	**Advantage of Tracrium** Clinical response unaffected by hepatic function[2] or patient age.[3] Duration of action can be prolonged with vecuronium in these patients.[4]









Total hip replacement	**Renal surgery**	**Neurosurgery for trauma**	**Everyday procedures**
Common patient type Elderly women and men	**Common patient type** Both adults and children	**Common patient type** Both adults and children	**Common patient type** Average
Advantage of Tracrium Recovery time unaffected by age.[3] With vecuronium, recovery time can be twice as long in the elderly.[5]	**Advantage of Tracrium** Recovery time unaffected by renal dysfunction.[2] With vecuronium, recovery time can be prolonged.[6]	**Advantage of Tracrium** Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).[7,8] The effect of vecuronium is decreased in patients receiving these agents.[8,9]	**Advantage of Tracrium** The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

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(atracurium besylate) 10 mg/mL

For more predictable recovery

See brief summary of prescribing information on adjacent page.

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

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THE SOCIETY FOR TECHNOLOGY IN ANESTHESIA

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STA invites participants to present abstracts at the meeting. The format for the Scientific Sessions will be Poster Presentation preceeded by one-minute (four-slide maximum) verbal summaries. The final deadline for submission is October 1, 1991. For more information regarding abstracts please contact: James H. Philip, MD, STA Scientific Chairman, 75 Francis Street, Boston, MA 02115; (617) 732-7330; Fax: (617) 732-6798; E-Mail 241-8308 @ MCI com.

For complete information regarding the Society for Technology in Anesthesia meeting in January, please contact Gerri Kuzava, Executive Secretary, STA, 128 East Court Street, Hastings, MI 49058; (800) 875-2525 or (616) 945-5110.

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References: 1. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology. 1982;56:112-118. 2. Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg. 1985;64:897-910. 3. Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology. 1986;65:A516. Abstract. 4. Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stresss associated with worse outcome? Anesthesiology. 1987;67:A1. Abstract. 5. Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology. 1987;66:130-135.

Predictable control of stress responses from induction through recovery

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***CONTROL** of the stress response is associated with less postoperative morbidity* [3,4]

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Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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March 1986, March 1987
U.S Patent No. 3,998,834
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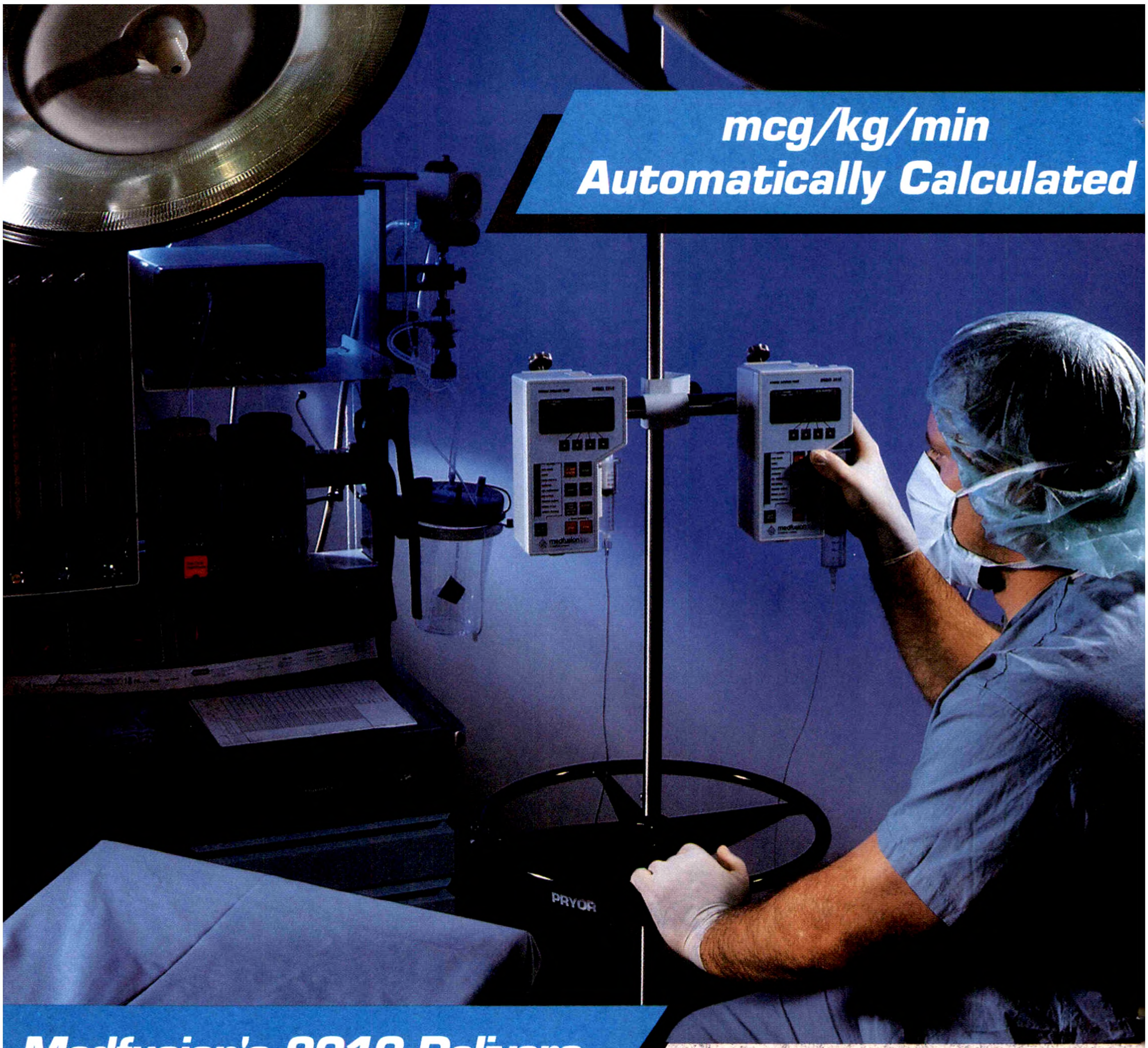

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Visceral Losses of Desflurane, Isoflurane, and Halothane in Swine

Michael J. Laster, DVM, Shahram Taheri, BS, Edmond I. Eger II, MD, Jin Liu, MD,
Ira J. Rampil, MD, and Roderick Dwyer, MB, FFARCS
Department of Anesthesia, University of California, San Francisco, California

Percutaneous loss of inhaled anesthetics is small relative to their uptake. The minor nature of this loss results in part from the substantial barrier to diffusion posed by the skin. Pleural and peritoneal surfaces pose less effective barriers because diffusion distances are smaller than in the skin. Accordingly, we measured visceral loss to air of desflurane, isoflurane, and halothane from pleural and peritoneal surfaces in five juvenile swine. Pleural and peritoneal losses per percent end-tidal anesthetic correlated directly with the solubility of the anesthetic in blood or tissues. The total pleural losses for the first 30 min of anesthetic administration were desflurane, 1.22 ± 0.22 mL (mean ± standard deviation for the 30-min period); isoflurane, 2.34 ± 0.52 mL; and halothane, 4.69 ± 0.98 mL; respective peritoneal losses were 0.64 ± 0.12 mL, 1.23 ± 0.25 mL, and 2.69 ± 0.57 mL. Pleural loss per unit time did not change with increasing duration of anesthesia, whereas peritoneal loss increased for all anesthetics. These visceral losses are greater than total percutaneous losses in humans given these anesthetics for the same period of time, but the loss of anesthetic by either route is too small to affect measurements of anesthetic kinetics or recovery.

(Anesth Analg 1991;73:209–12)

Percutaneous loss of inhaled anesthetics is a trivial fraction of the total amount of the anesthetic taken up by the body (1–3). Three considerations suggest that losses from the visceral surfaces in the abdomen or thorax during intraabdominal or thoracic surgery might be considerably larger than percutaneous losses: (a) the hard outer layer of skin (stratum corneum) may form a less pervious barrier; (b) skin forms a thicker barrier to diffusion than peritoneal or pleural membranes; and (c) blood flow to viscera is greater than blood flow to skin. Cullen and Eger (4) have shown a greater rate of diffusion of anesthetics through membranes similar to the pleural and peritoneal membranes than through skin. However, two factors may limit visceral losses relative to percutaneous losses: (a) the surface area of skin is larger than the surface of the viscera exposed during surgery (unless the bowel is exteriorized and exposed to air); and (b) the period of exposure of viscera during surgery is limited, whereas percutaneous losses continue throughout anesthesia and throughout the period of recovery (2,3). In the present study, we measured losses of inhaled anesthetics in swine from their abdominal and thoracic viscera. If great, such losses in patients may contribute to the contamination of the operating room environment. They also may influence the total uptake of anesthetic.

Methods

With approval of our Committee on Animal Research, we studied five juvenile swine (2.5–3 mo old; 30–35 kg). Pentobarbital was given intravenously or intramuscularly in amounts sufficient to induce anesthesia (20–40 mg/kg). In three animals, this was sufficient to permit endotracheal intubation. In the remaining two, succinylcholine was used to facilitate intubation. After intubation, each pig was maintained supine with a 45° tilt to the left to permit insertion of catheters into the pleural and peritoneal cavities. This position was maintained for the remainder of the study. The endotracheal tube was connected through a sampling fitting to a conventional anesthetic circle absorption system having a 5-cm positive end-expiratory pressure valve (Vital Signs, Totowa, N.J.) on the expiratory limb of the circuit. Oxygen was delivered to the circuit at a flow rate of 1 L/min. Ventilation was controlled to produce an

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Supported in part by the Anesthesia Research Foundation and in part by Anaquest.
Accepted for publication April 8, 1991.
Address correspondence to Dr. Eger, Department of Anesthesia, S-455, University of California, San Francisco, CA 94143-0464.

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0003-2999/91/$3.50

end-tidal CO_2 of 4%–4.5%. Gas samples drawn from the sampling fitting were analyzed for CO_2 using a Datex 254 infrared analyzer (Puritan-Bennett, Wilmington, Mass.). If not inserted before anesthesia, an intravenous catheter was inserted after induction of anesthesia. Until administration of the inhaled anesthetics, we maintained anesthesia with intermittent intravenous injections of pentobarbital (200–300 mg). A rectal temperature probe was inserted. Temperature was monitored and was maintained with heating lamps or pads at 38.2 ± 0.2°C throughout each study. An arterial catheter was inserted into the femoral or auricular artery, and arterial blood pressure was transduced. Arterial blood pressure was maintained above 90/60 mm Hg throughout each study.

Four catheters (3.5-mm internal diameter) were inserted 2–3 cm into the pleural and peritoneal cavities (two per cavity) through small (about 3 cm) incisions in the abdominal and thoracic walls. The distance between the incisions was made as great as the structure of each cavity permitted, and the catheter tips were directed away from each other. The incisions were sutured closed to provide an air-tight seal. One catheter per cavity was connected to a flowmeter that delivered air at a calibrated flow rate of 1.2 L/min. The remaining catheters conducted the gases from the respective cavities. Each of these effluent catheters was attached to a "T" connector having a three-way stopcock mounted on one end for gas sampling. The other end was connected to an underwater seal of 3-cm height.

We prepared tanks containing mixtures of anesthetic vapors in oxygen. These were 1.9% desflurane, 0.4% isoflurane, and 0.2% halothane, the combination giving an anesthetic mixture totaling about 1 MAC. Concentrations were analyzed using a Gow-Mac (Gow Mac Instrument, Bridgewater, N.J.) flame ionization detector gas chromatograph equipped with a 3-m-long, stainless steel column (3.2-mm internal diameter) packed with Chromosorb-WHT 60-80 mesh maintained at 50°C. A nitrogen carrier stream flowed at 13 mL/min through the column to a flame ionization detector at 130°C, supplied by hydrogen at 33 mL/min and by air at 250 mL/min, and equipped with a 0.1-mL sample loop for high concentrations. Results were recorded on a strip-chart recorder. The chromatograph was calibrated using secondary tank standards that had been calibrated with primary standards produced by injection of a liquid aliquot of anesthetic by micropipette into a flask of known volume. Peak heights were proportional to concentration over the entire range of concentrations studied, and linearity was confirmed over the range of concentrations measured.

For control purposes, duplicate samples of gas were drawn (with a 10-min interval between samples) from the fitting at the endotracheal tube (end-tidal concentration or F_E), and the stopcocks at the catheters leaving the abdomen (F_{ABD}) and thorax (F_{TX}). These control samples were analyzed by gas chromatography to determine if any contaminant peaks cochromatographed with the anesthetic peaks to be analyzed. Although contaminant peaks were found, they either had retention times that differed from those of the anesthetics, or their peak heights were trivial fractions of the smallest experimental peak heights (<5%).

After completion of the surgical preparation, the oxygen inflow was halted and the tank containing the gas mixture of desflurane, halothane, and isoflurane was connected to the anesthetic circuit. A flow of 4.5 L/min was introduced into the anesthetic circuit for the first 20–30 min of administration. Flow thereafter was reduced to 2 L/min for the remaining duration of the study (120 min). These flows were sufficient to sustain a constant mean end-tidal concentration of the vapors as indicated by the readout from the Datex analyzer. Samples of gas for determination of F_E, F_{ABD}, and F_{TX} were taken every 10 min into 50-mL glass syringes sealed with Nylon stopcocks. The syringes were stored upright until their gas contents were analyzed by gas chromatography.

At the end of each experiment, we performed an autopsy to verify appropriate placement of each catheter. We also examined the lung and abdominal contents to document that placement of the catheters had not resulted in injury.

The anesthetic gas concentrations obtained by gas chromatography were normalized as follows. Ratios of F_{ABD}/F_E and F_{TX}/F_E were calculated for the data from each set of samples. Values for the mean and standard deviation were determined for each point in time for each ratio and were plotted against time. Using a paired Student's t-test, the resulting mean values then were compared to determine differences among anesthetics and between the results for abdomen versus thorax for a given anesthetic. Examination of these data indicated considerable variability in the values from the samples taken at 10 and 20 min, with thoracic values being higher than subsequent values and abdominal values being lower. We performed regression analyses on the values from 40 to 120 min for each pig.

We calculated milliliters of anesthetic lost per 10-min period at a 1% F_E from the abdomen and thorax separately as 120 times the F_{ABD}/F_E and 120 times F_{TX}/F_E, respectively (i.e., 1200 $mL\cdot min^{-1} \times 10$ min $\times$ 0.01; the 0.01 is 1% rendered as a fractional percentage). The cumulative losses for 30, 60, and 120 min also were calculated. Using a paired Student's t-test, we compared the resulting mean values to determine differences among anesthetics and between the results for abdomen versus thorax for a given anesthetic.

Table 1. Cumulative Loss of Anesthetic

Anesthetic	Pleural loss			Peritoneal loss		
	30 min	60 min	120 min	30 min	60 min	120 min
Desflurane	1.22 ± 0.22	2.27 ± 0.36	4.38 ± 0.71	0.64 ± 0.12	1.37 ± 0.17	2.92 ± 0.30
Isoflurane	2.34 ± 0.52	4.41 ± 0.82	8.58 ± 1.32	1.23 ± 0.25	2.65 ± 0.52	5.76 ± 1.07
Halothane	4.69 ± 0.98	8.62 ± 1.47	16.6 ± 2.4	2.69 ± 0.57	5.71 ± 1.20	12.3 ± 2.6

Values are given as the mean ± SD of the total milliliters of anesthetic lost for the period indicated, normalized to the end-tidal concentration of anesthetic. That is, the values are the losses that would have occurred if the end-tidal concentration had been 1%. All values at each point in time were significantly different among anesthetics (P at least <0.002 for all comparisons). Similarly, for a given anesthetic, peritoneal loss was always less than pleural loss ($P < 0.01$).

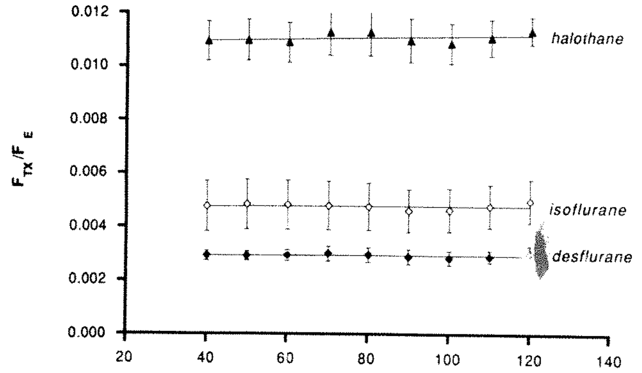

Figure 1. Pleural loss of halothane, isoflurane, and desflurane, reflected in the fraction of the concentration in the 1.2 L/min of gas flowing through the intrapleural cavity (F_{TX}) to the end-tidal concentration (F_E) of each anesthetic, was constant over the period of 40–120 min of anesthetic administration. Loss was greatest for halothane, less for isoflurane, and least for desflurane. Values at each point are the mean ± SD.

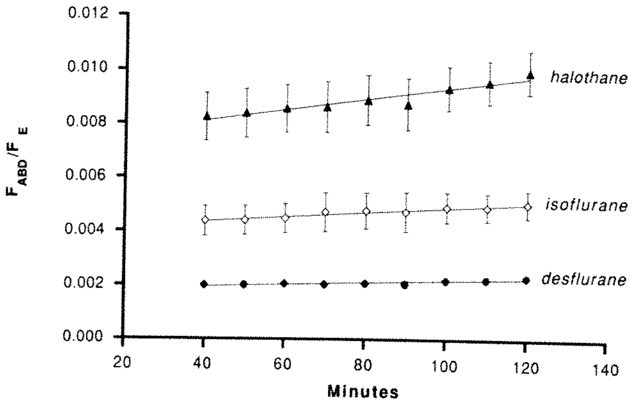

Figure 2. Peritoneal loss of halothane, isoflurane, and desflurane, reflected in the fraction of the concentration in the 1.2 L/min of gas flowing through the peritoneal cavity (F_{TX}) to the end-tidal concentration (F_E) of each anesthetic, increased over the period of 40–120 min of anesthetic administration. Loss at any given point in time was greatest for halothane, less for isoflurane, and least for desflurane. Values at each point are the mean ± SD.

To compensate for the multiple comparisons made among the three anesthetics, we accepted $P < 0.01$ as statistically significant (Bonferroni correction).

Results

End-tidal concentration was acceptably stable over the course of anesthetic administration, increasing less than 10% with the most soluble agent, halothane, in the period from 30 to 120 min. End-tidal concentration increased less with isoflurane (8.1%) and least with desflurane (5.5%).

Differences among anesthetics and between thorax and abdomen were statistically different (Table 1). Losses from both cavities were greatest with halothane, less with isoflurane, and least with desflurane (Table 1, Figures 1 and 2). That is, F_{ABD}/F_E and F_{TX}/F_E were halothane > isoflurane > desflurane. The absolute cumulative volume losses at 30, 60, or 120 min paralleled this order. Regression analysis showed that loss from the thoracic cavity did not change after 40 min for any anesthetic (Figure 1), but loss from the abdomen increased throughout the period from 40 to 120 min (Figure 2). For pleural losses over time, the square of the correlation coefficient (r^2) for desflurane was 0.006, isoflurane 0.001, and halothane 0.15, indicating the absence of a deviation of these slopes from zero. For the abdominal losses, the r^2 for desflurane was 0.85, isoflurane 0.94, and halothane 0.91, indicating the absence of equilibration. Loss from the peritoneum always was less than loss from the pleura (Table 1).

Discussion

The order of magnitude of visceral loss reflects the differences in the solubilities of the agents tested. The least soluble agent, desflurane, had the least loss per percent end-tidal concentration, and the most soluble agent, halothane, had the greatest loss. These results are consistent with percutaneous results and are explained by the greater diffusivity associated with increasing solubility.

Pleural losses reached a steady state during the 120-min course of administration (Figure 1). In contrast, losses from the peritoneum were lower and did not reach equilibrium (Figure 2). Several factors might explain these differences. First, much of the transfer in the lungs is not limited by perfusion; anesthetic can pass directly from alveoli through the pleural surface. Second, the storage capacity of fat within the abdominal cavity might have limited the partial pressure of anesthetic available for transfer, in addition to which the partial pressure of anesthetic available for diffusion is limited by perfusion; that is, by the rate at which anesthetic is delivered to the viscera.

The visceral losses as loss per the first 30-min interval, normalized to 1% end-tidal anesthetic concentration equaled (peritoneal) or exceeded (pleural) the percutaneous loss in humans for the same anesthetic [measured in a separate study (2)]. The total percutaneous losses obtained in humans were desflurane, 0.42 ± 0.18 mL (at 1% end-tidal desflurane); isoflurane, 1.16 ± 0.43 mL; and halothane 2.28 ± 0.71 mL. Our values for peritoneal losses were (Table 1) 0.64 ± 0.12 mL, 1.23 ± 0.25 mL, and 2.69 ± 0.57 mL for the respective anesthetics; for pleural losses we found values of 1.22 ± 0.22 mL, 2.34 ± 0.52 mL, and 4.69 ± 0.98 mL. As suggested in the introduction, this greater visceral loss probably resulted from the diminished barrier to diffusion posed by the peritoneal and pleural membranes and by the greater flow of blood to the viscera. Percutaneous losses from pigs have not been measured, and thus a similar comparison cannot be made for swine data.

We also may consider the similarities and differences between our experimental conditions and those that might apply to a patient undergoing intraabdominal or thoracic surgery. We believe our experimental model approximated a human whose pleural or peritoneal cavities were opened to expose the surface of a layer of intestine or the surface of the lung. We deliberately imposed a back-pressure of 3 cm of water to raise the abdominal wall from the viscera and to separate the parietal and visceral pleural surfaces without producing compromise of the circulation (as indicated by maintenance of blood pressure). The flow of air (1.2 L/min) over these exposed surfaces was sufficient to clear the anesthetic that had diffused from the visceral surfaces (i.e., it was sufficient to eliminate any back-pressure) and thus approximated the condition found in the operating room where the circulation of air over the intestine or lung would similarly clear any anesthetic.

Our model may underestimate visceral losses in humans for various reasons. The larger cavity of an adult human would provide a larger surface area. This might be increased further if the viscera were exteriorized. On the other hand, a decrease in exposed surface area would result from a smaller incision or the packing away of the viscera. Thus, it is difficult to estimate whether our results would be increased or decreased in the clinical milieu.

Although visceral losses can exceed percutaneous losses, neither are of sufficient magnitude to affect anesthetic uptake or the concentration of anesthetic in the operating room. During the first half hour of anesthesia administration in volunteers, uptake (per percent inspired concentration) of desflurane is 206 ± 30 mL (5), of isoflurane 388 ± 115 mL (5) or 393 ± 52 mL (6), and of halothane 560 ± 60 mL (5). These values are two to three times those found in 20-kg swine: uptake of desflurane is 75 ± 12 mL, of isoflurane 121 ± 21 mL, and of halothane 223 ± 23 mL [N. Yasuda (personal communication from unpublished data) and see (7)]. Regardless of which values are accepted, uptake of a given agent during the first 30 min of anesthesia is approximately 100 times as great as loss from the pleura or peritoneum, which supports the argument that visceral losses will not materially influence the demands placed on anesthetic delivery.

The considerations discussed in the preceding paragraph also speak to the rationale for the choice of the pig as the experimental model for the study of visceral losses. Pigs are approximately the same size as humans (our pigs being half the size of an adult human) and have anatomy and circulatory variables that parallel those found in humans. For example, in pigs, cardiac output during anesthesia with volatile agents is 65–100 $mL \cdot kg^{-1} \cdot min^{-1}$, comparable to that found in adult patients, and the perfusion of viscera in pigs is not dissimilar to that found in humans (8,9).

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Simultaneous Comparison of Intraarterial, Oscillometric, and Finapres Monitoring During Anesthesia

Nathan L. Pace, MD, and Thomas D. East, PhD

Department of Anesthesiology, University of Utah, Salt Lake City, Utah

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In 30 patients (15 with normal peripheral vascular status and 15 with peripheral vascular disease, hypertension, or a heavy smoking history), systolic, mean, and diastolic arterial pressures were recorded simultaneously every 5 min using a radial arterial catheter, an oscillometric arm cuff, and a Finapres finger cuff during 1–6 h of anesthesia and operation. The average accuracy of oscillometric and Finapres pressure measurements was good. Comparisons of arterial, oscillometric, and Finapres pressures showed only a small bias in the oscillometric and Finapres pressure estimations. Finapres pressures underestimated arterial pressures by 1 mm Hg more than oscillometric pressures did. Peripheral vascular status had no effect on comparisons made between pressures measured with these two techniques. Although bias was small, precision was often lacking as shown by the large variability of the difference between individual values from the three monitors. However, the precision of Finapres pressure measurements was about the same order of magnitude as that of oscillometric measurements.

(Anesth Analg 1991;73:213–20)

The Finapres is a noninvasive blood pressure monitor using a finger cuff; it provides a nearly continuous beat-to-beat pressure waveform and digital display of systolic, mean, and diastolic pressures. The principle of measurement is known as "pressure following"; pressure values tend to be 5 mm Hg less than directly measured radial artery pressures (1). The technique for measurement of blood pressure based on this principle was first proposed by Penaz in 1973 (2) and was subsequently developed as the Finapres monitor by a research group in The Netherlands (3). The Finapres has been refined and clinically tested in anesthetized, critically ill, and healthy patients and in volunteers (4–10). In previous studies, Finapres (FINA) has been compared with either a radial artery (ART) pressure monitor (through an intravascular catheter) or an oscillometric (OSC) upper arm pressure cuff, but only two previous studies (7,11) compared all three pressure measurement techniques simultaneously.

Previous studies have also focused on finding the optimal conditions for good FINA performance. Kurki et al. (8) suggested that differences in pressure readings between FINA and ART techniques were caused by factors affecting peripheral blood flow such as the use of vasoconstrictors or the presence of peripheral vascular disease. The purpose of this study was to compare pressures measured simultaneously during anesthesia using all three techniques in patients with and without conditions affecting the peripheral vascular system.

Methods

Study Design

Thirty-six patients scheduled for elective surgical procedures at the University of Utah Hospital during which radial artery catheterization was to be used were recruited for this study. The study protocol was approved by the University of Utah Health Sciences Center Institutional Review Board, and written and oral informed consent was obtained from each patient. Patients with a known asymmetry in arm blood pressures were not recruited into the study. The management of anesthesia care was at the discretion of the attending anesthesiologist and was not directed by personnel collecting pressure data; general anesthesia was used. Data collection was performed during the maintenance of anesthesia for one or more hours.

Supported by a grant from the Ohmeda Corporation, Denver, Colorado.

Presented in part at the annual meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 1987.

Accepted for publication February 22, 1991.

Address correspondence to Dr. Pace, Department of Anesthesiology, 3C-444, University of Utah, 50 North Medical Drive, Salt Lake City, UT 84132.

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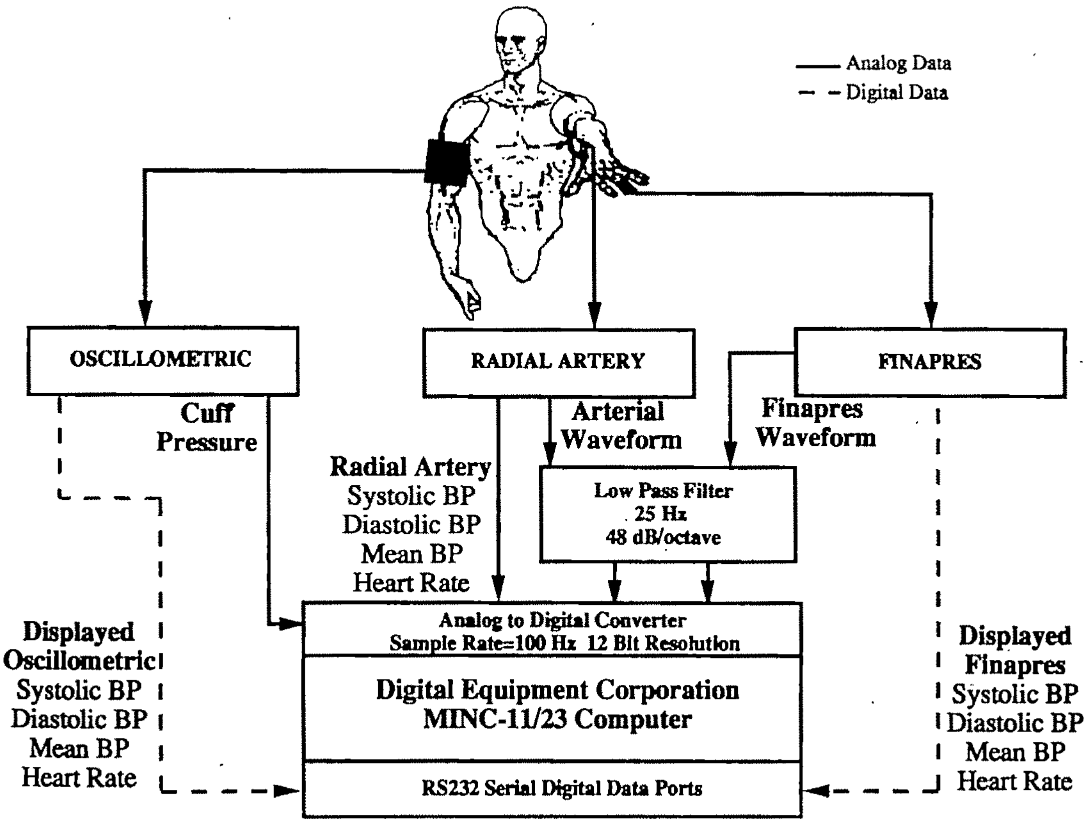
Analog Data
Digital Data
OSCILLOMETRIC
RADIAL ARTERY
FINAPRES
Cuff Pressure
Arterial Waveform
Finapres Waveform
Radial Artery Systolic BP Diastolic BP Mean BP Heart Rate
Low Pass Filter 25 Hz 48 dB/octave
Analog to Digital Converter Sample Rate=100 Hz 12 Bit Resolution
Digital Equipment Corporation MINC-11/23 Computer
RS232 Serial Digital Data Ports
Displayed Oscillometric Systolic BP Diastolic BP Mean BP Heart Rate
Displayed Finapres Systolic BP Diastolic BP Mean BP Heart Rate

Figure 1. Block diagram of Finapres evaluation system.

Data Collection

Each patient was instrumented with the three monitoring devices. A 20-gauge Teflon catheter was inserted percutaneously into a radial artery and connected through a 1.2-m, 1.5-mm-diameter stiff Teflon tube to a Gould disposable pressure transducer. A continuous flush device was used. The pressure transducer was connected to a Tektronix 414 Portable Patient Monitor (Tektronix, Beaverton, Ore.). The FINA (Ohmeda Monitoring System, Englewood, Colo.) cuff was wrapped around the middle phalanx of the middle finger of the arm with the intraarterial catheter. A standard adult OSC blood pressure cuff was placed on the contralateral arm from the intraarterial catheter. Oscillometric blood pressure was measured automatically every 5 min using the Dinamap model 845XT Vital Signs Monitor (Critikon, Tampa, Fla.).

Maximal OSC cuff deflation time was 45 s; a 45-s block of simultaneous waveform data from all three monitors was collected every 5 min at each OSC cuff deflation. In addition, at the completion of the OSC cuff deflation, the most recent digitally displayed values of systolic, mean, and diastolic pressures were collected from the OSC and FINA monitors (RS-232 serial ports) and from the ART monitor (analog port). All data were stored electronically.

Data Handling and Processing

The system shown in Figure 1 was used to collect blood pressure data simultaneously from all three monitors. The ART and FINA pressure waveforms were low pass filtered at 25 Hz using a Krohn-Hite 48 dB/octave active filter (Krohn-Hite Corporation, Avon, Mass.) to avoid aliasing. These two signals as well as the OSC cuff pressure were sampled at 100 Hz using a MINC-11 computer (Digital Equipment Corporation, Maynard, Mass.) during the periodic (every 5 min) OSC cuff deflation.

The Dinamap monitor was calibrated before the study started. Just before the initiation of data collection, four separate calibration checks were performed during the first OSC cuff deflation. First, the arterial catheter was flushed at 300 mm Hg, and the flush pressure was released rapidly to "flick" or "square wave" test the frequency response of the arterial line and transducer (12). Second, the 100-mm Hg calibration button on the Tektronix monitor was activated. Third, the pressure transducer was zeroed. Fourth,

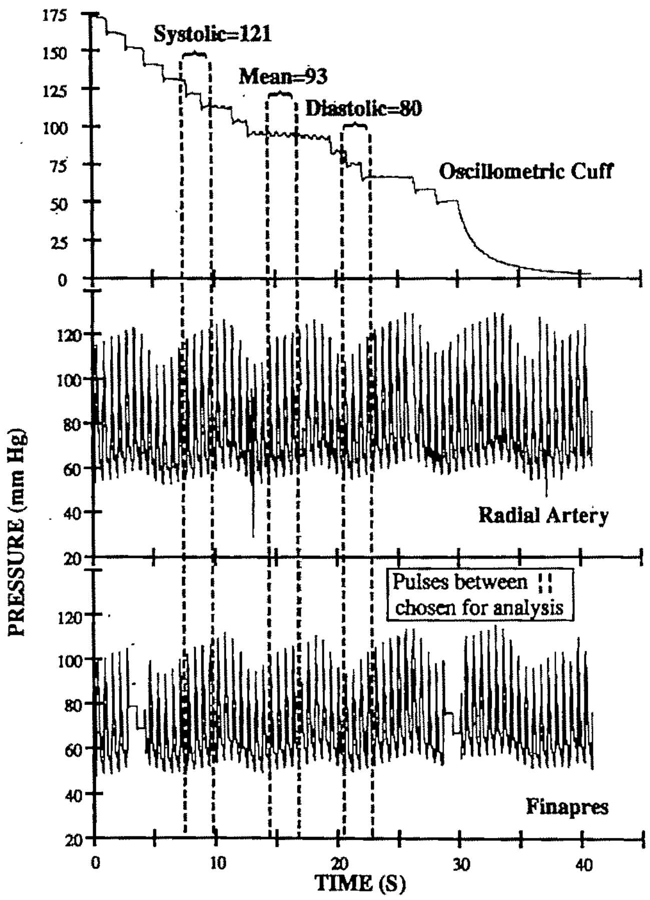

Figure 2. Typical strip chart recording of pressure waveforms during OSC cuff deflation. The digital values represent the pressures asserted by the OSC algorithm for that cuff deflation cycle. The *vertical dashed lines* denote the epochs of the ART and FINA waveforms chosen for analysis.

the FINA calibration test was activated, which produced a series of 100-mm Hg square pulses. Typically, the calculated overall system resonant frequency of the ART pressure was 17 Hz, and the damping coefficient was about 0.17. This transient response includes the pressure transducer/catheter system as well as the electronics in the Tektronics monitor and in the 25-Hz low pass filter. Therefore, this response is difficult to interpret using a simple second-order model routinely used to specify such a transient response. It does indicate that the system has an adequate response time and was not excessively damped by other factors (e.g., air bubbles).

Figure 2 illustrates the waveforms collected during a typical OSC cuff deflation and illustrates the derivation of pressures from the waveforms. The OSC analog signal was used to synchronize the derivation of FINA and ART pressures. To reduce respiratory artifact, the four heart beats from the FINA and ART pressure that bracketed the instant at which the OSC device sent in succession the systolic, mean, and diastolic pressures from the OSC cuff pressure were identified. If no peaks (maximum) or troughs (minimum) in pressure were detected in the ART waveform and no corresponding maxima/minima were detected in the FINA waveform, then that particular cardiac cycle was considered to be missing. A simple peak detection algorithm based on a smoothed derivative was used to identify systolic and diastolic pressures on each of the available ART and FINA waveforms, and mean pressure was calculated by numerical integration for each cardiac cycle. These waveform-derived ART and FINA systolic, mean, and diastolic pressures for each OSC cycle were the averages of the appropriate pressure from the four or less available cardiac cycles analyzed for each pressure of each OSC deflation. In addition, limits were placed on the absolute values for diastolic (20–180 mm Hg) and systolic (20–250 mm Hg) pressures. Values measured outside this range were considered to be artifact and the variable was assigned a missing value code.

Statistical Analysis

The analysis followed the suggestions of Altman and Bland (13,14) as amplified by Chinn (15). Data analysis was performed on both digitally displayed and waveform-captured variables. The 15 variables analyzed included systolic, diastolic, and mean pressures for OSC, for digital and waveform ART, and for digital and waveform FINA. Analysis of the waveform data allowed a comparison of the pressures without any possible artifacts of differences in update rates of digital displays. No attempt was made to transform the scale of measurement of the 15 variables. Patients were modeled as a random effects factor.

Radial artery pressure measured through an intraarterial catheter was considered to be the standard against which FINA and OSC pressures should be compared. This totaled 2 × 2 × 3 = 12 comparisons (ART versus FINA and ART versus OSC for systolic, mean, and diastolic pressures derived from both display and waveform data). Accuracy was estimated (see Appendix for details of statistical methods); the mean difference, also known as bias, between new and old values shows whether the new method overestimates or underestimates values obtained by the old method. Agreement of FINA and OSC pressures (the new methods) with ART pressures (the standard method) was performed by subtracting FINA and OSC pressures from ART pressures. The standard deviation of the individual differences is used to specify the precision of agreement by calculating the 95% range for the limits of agreement (bias ± 2 × standard deviation). Global tests using all data were undertaken. The effects on bias of the presence or absence of vascular disease, the choice of noninvasive monitor, digital versus waveform data, systolic versus mean versus diastolic pressure, and pressure level were estimated by a mixed-model analysis of covariance.

The statistical software was from BMDP (BMDP Statistical Software, Los Angeles, Calif.). The program modules used included 1D (simple data description), 3D (*t*-tests), 5D (histograms), 6D (scatterplots), and 3V (random effects and mixed-model ANOVA and ANCOVA). A $P < 0.05$ was set for statistical significance. Statistical graphs were created in SYSTAT (SYSTAT, Evanston, Ill.).

Results

The data were available for analysis only in 30 subjects for a variety of reasons, including data recording failure and short duration of operation. Fifteen of the 30 patients had a normal peripheral vascular status; 15 had either peripheral vascular disease (5 patients) or a condition likely to affect the peripheral vascular system such as heavy smoking or hypertension (10 patients). The total number of data sets available for analysis was 1227 and ranged from as few as 12 data sets to as high as 68 data sets per patient.

Based on all data, the overall bias or difference between noninvasive pressure and invasive pressure determinations was −0.3 ± 1.6 mm Hg (mean ± SE); this was not statistically different from zero (95% confidence interval, −3.4 to 2.8 mm Hg). There was no effect of peripheral vascular disorders on bias. There were statistically significant differences between FINA and OSC: FINA pressure underestimated ART pressure by 1.3 ± 0.1 mm Hg more than OSC pressure did. The bias from analog waveforms averaged 1.0 ± 0.1 mm Hg more positive than that from the digital display. There was a small effect of the pressure level on bias—a 0.5-mm Hg increase in bias for each 10-mm Hg increase in pressure. There was a difference in the amount of bias between systolic, mean, and diastolic pressures.

Table 1 displays all 12 comparisons of devices. Examination of the individual biases confirms the global statistical results. The bias of FINA values was always more positive than that of OSC values. The bias of analog waveform data was consistently offset by several millimeters of mercury from that of digital display data. The bias decreased from most positive in systolic pressure to most negative in diastolic pressure with mean pressure bias being intermediate. Nevertheless, these biases were statistically significant (both digital and analog waveform) only for FINA systolic and OSC diastolic pressures. There was no statistically significant bias in mean pressure. The limits of agreement for all comparisons can only be described as generously large. The limits of agreement for analog waveform values were always smaller than that for digital display values.

Table 1. Comparisons Analysis

Pressure	Bias (mean ± SE)	95% Confidence interval of bias	95% Range of limits of agreement
Digital display			
Systolic			
OSC	−0.6 ± 2.7	−6.0 to 4.8	−27.1 to 26.0
FINA	5.8 ± 2.5[a]	0.8 to 10.7	−22.9 to 34.4
Mean			
OSC	−0.7 ± 1.9	−4.4 to 3.1	−21.6 to 20.3
FINA	0.6 ± 1.6	−2.6 to 3.8	−18.7 to 20.0
Diastolic			
OSC	−6.3 ± 1.9[a]	−10.0 to −2.5	−32.3 to 19.7
FINA	−5.4 ± 1.7[a]	−8.7 to −2.1	−31.1 to 20.2
Analog waveform			
Systolic			
OSC	0.7 ± 2.7	−4.6 to 6.1	−18.8 to 20.2
FINA	8.8 ± 2.2[a]	4.5 to 13.2	−9.1 to 26.8
Mean			
OSC	−0.1 ± 1.8	−3.8 to 3.6	−15.0 to 14.8
FINA	1.8 ± 1.5	−1.1 to 4.7	−8.7 to 12.3
Diastolic			
OSC	−4.3 ± 1.9[a]	−8.0 to −0.6	−14.9 to 6.3
FINA	−2.6 ± 1.5	−5.6 to 0.3	−11.8 to 6.6

The units are mm Hg. The bias is given as invasive minus noninvasive pressure.

[a] The statistical significance ($P < 0.05$) of a bias ≠ zero.

Dual histograms of bias for OSC and FINA pressures show that the distributions of pressure differences appear similar. This is true whether the distribution is peaked (Figure 3, diastolic pressure) or broad (Figure 4, systolic pressure). Figures 5 and 6 display the limits of agreement for one OSC and one FINA comparison; neither show any marked effect of average pressure on bias.

The bias for individual patients is shown in Table 2. The superscript "*a*'s" indicate those mean differences that were statistically significant from zero. There was an extraordinarily wide range of offsets among the patients. For example, one patient had an OSC systolic pressure that averaged 42 mm Hg higher than ART systolic pressure, whereas another patient had an OSC systolic pressure that averaged 25 mm Hg lower than ART systolic pressure. The bias range noted among patients was from −42 mm Hg to +30 mm Hg. This wide range in biases existed for both OSC and FINA pressures.

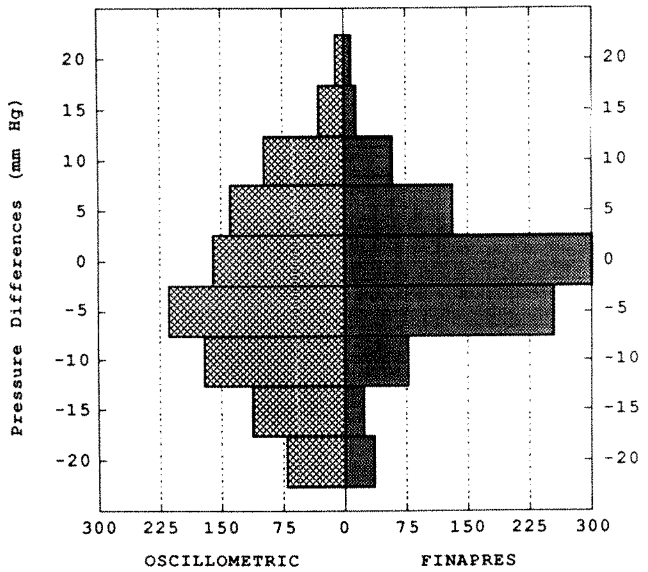

Figure 3. Dual histogram of the distribution of pressure differences between ART versus OSC and ART versus FINA diastolic pressures; analog waveform data are used. Each *bar* is a count of the number of differences centered at that pressure.

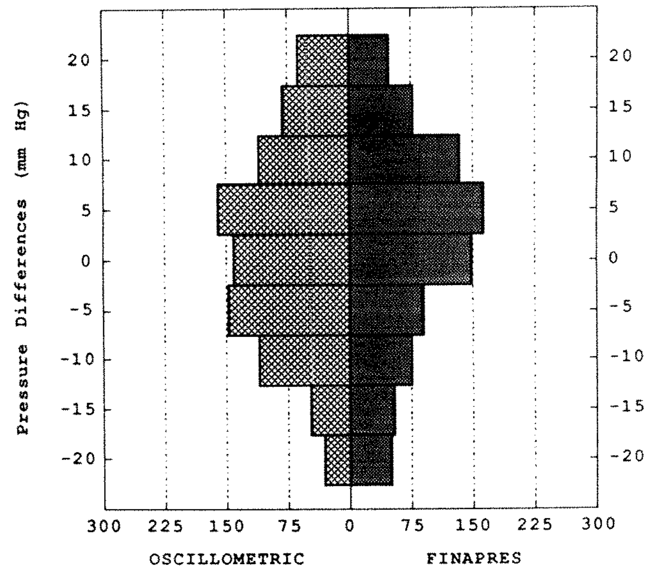

Figure 4. Dual histogram of the distribution of pressure difference between ART versus OSC and ART versus FINA systolic pressures; digital display data are used. Each *bar* is a count of the number of differences centered at that pressure.

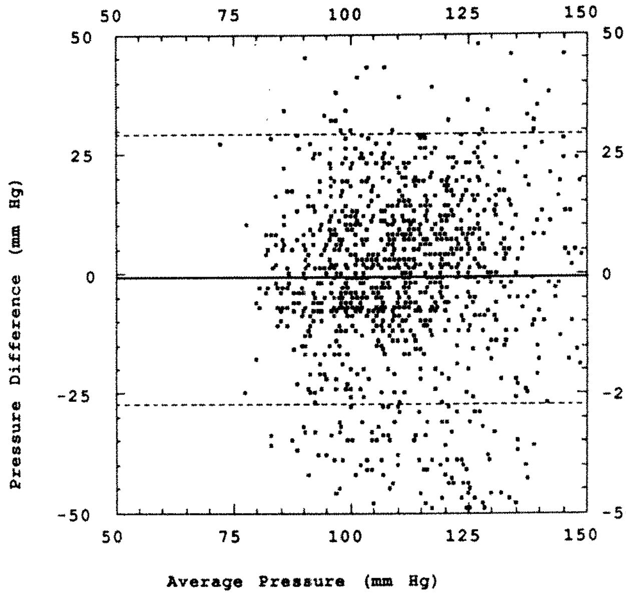

Figure 5. Scatterplot of OSC and ART (difference vs average) for systolic pressure; digital display data are used. The *solid horizontal line* is the mean bias; the *two dashed lines* are the upper and lower bounds of the 95% limits of agreement.

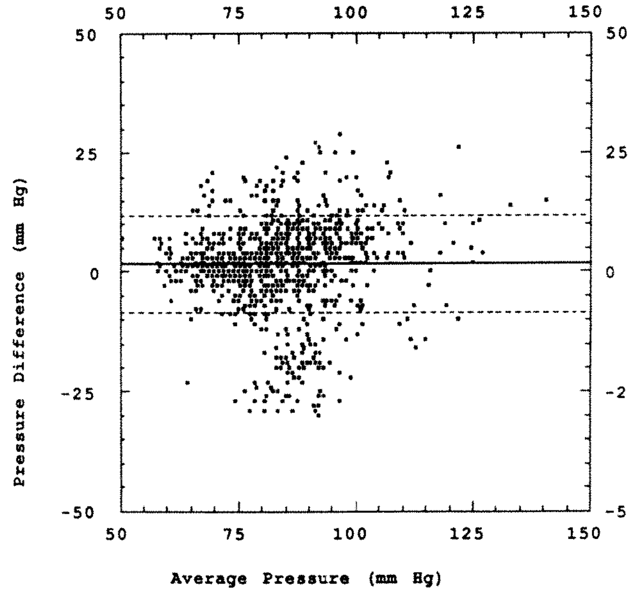

Figure 6. Scatterplot of ART and FINA (difference vs average) for mean pressure; analog waveform data are used. The *solid horizontal line* is the mean bias; the *two dashed lines* are the upper and lower bounds of the 95% limits of agreement.

Discussion

Statistical Methods

New monitors, such as noninvasive blood pressure devices, are studied with the hope that their readings are interchangeable with a monitor already in use (invasive blood pressures) and that among other factors their cost is less, their results are more timely, and they place the patient at less risk. The best type of analysis to decide interchangeability has been unclear in the past. Previous studies have favored statistical techniques oriented toward calibration problems and have used regression and correlation methods. There are strong reasons to choose alternative statistical techniques for the comparison of mea-

Table 2. Pressure Offset by Patient

Systolic pressure		Mean pressure		Diastolic pressure	
OSC	FINA	OSC	FINA	OSC	FINA
−42 ± 9[a]	−21 ± 4[a]	−25 ± 5[a]	−26 ± 3[a]	−31 ± 5[a]	−28 ± 3[a]
−34 ± 5[a]	−14 ± 13[a]	−16 ± 8[a]	−15 ± 5[a]	−20 ± 3[a]	−19 ± 9[a]
−19 ± 8[a]	−11 ± 5[a]	−11 ± 7[a]	−8 ± 7[a]	−16 ± 6[a]	−18 ± 6[a]
−14 ± 25[a]	−5 ± 8[a]	−9 ± 10[a]	−6 ± 16	−15 ± 5[a]	−10 ± 14[a]
−11 ± 11[a]	−4 ± 5[a]	−9 ± 6[a]	−5 ± 5[a]	−13 ± 3[a]	−9 ± 3[a]
−6 ± 12[a]	−2 ± 5	−7 ± 16	−2 ± 7	−12 ± 3[a]	−7 ± 4[a]
−6 ± 9[a]	−1 ± 12	−7 ± 10[a]	−1 ± 8	−10 ± 4[a]	−7 ± 3[a]
−3 ± 10[a]	−0 ± 5	−7 ± 6[a]	−1 ± 4	−9 ± 10[a]	−5 ± 6[a]
−2 ± 15	3 ± 9[a]	−5 ± 9	−1 ± 2[a]	−9 ± 3[a]	−5 ± 4[a]
−2 ± 4[a]	3 ± 10	−4 ± 14	−0 ± 2	−8 ± 5[a]	−4 ± 3[a]
−1 ± 5	5 ± 4[a]	−3 ± 8[a]	1 ± 1[a]	−8 ± 3[a]	−4 ± 2[a]
−1 ± 5	6 ± 4[a]	−3 ± 8[a]	1 ± 5	−7 ± 6[a]	−2 ± 6[a]
0 ± 9	8 ± 5[a]	−3 ± 5[a]	1 ± 9	−7 ± 6[a]	−2 ± 3[a]
1 ± 8	9 ± 3[a]	−2 ± 4[a]	2 ± 3[a]	−7 ± 3[a]	−1 ± 5
2 ± 9	9 ± 6[a]	−1 ± 10	2 ± 5	−6 ± 4[a]	−1 ± 3
2 ± 14	10 ± 8[a]	−1 ± 4	3 ± 2[a]	−5 ± 4[a]	−1 ± 2
3 ± 5[a]	10 ± 14[a]	−0 ± 8	3 ± 6[a]	−4 ± 3[a]	−1 ± 2[a]
4 ± 7[a]	12 ± 9[a]	0 ± 8	4 ± 2[a]	−3 ± 4[a]	−1 ± 2[a]
4 ± 8[a]	12 ± 11[a]	1 ± 4[a]	4 ± 3[a]	−2 ± 8	−0 ± 4
5 ± 8[a]	14 ± 6[a]	1 ± 5	4 ± 5[a]	−2 ± 7	−0 ± 3
7 ± 11[a]	15 ± 5[a]	1 ± 9	5 ± 3[a]	−2 ± 6	−0 ± 2
8 ± 7[a]	15 ± 9[a]	6 ± 6[a]	5 ± 4[a]	1 ± 7	1 ± 4
8 ± 22	16 ± 10[a]	7 ± 6[a]	5 ± 6[a]	2 ± 7	3 ± 3[a]
9 ± 11[a]	19 ± 3[a]	7 ± 12[a]	6 ± 3[a]	5 ± 4[a]	3 ± 5[a]
12 ± 8[a]	21 ± 10[a]	8 ± 3[a]	10 ± 3[a]	6 ± 4[a]	3 ± 4
13 ± 7[a]	23 ± 43	10 ± 5[a]	10 ± 5[a]	6 ± 5[a]	5 ± 3[a]
15 ± 10[a]	26 ± 12[a]	13 ± 7[a]	11 ± 3[a]	8 ± 3[a]	5 ± 4[a]
21 ± 7[a]	27 ± 10[a]	17 ± 6[a]	11 ± 7[a]	10 ± 4[a]	6 ± 3[a]
25 ± 7[a]	29 ± 7[a]	18 ± 11[a]	14 ± 6[a]	10 ± 6[a]	6 ± 9[a]
25 ± 9[a]	30 ± 6[a]	20 ± 7[a]	15 ± 9[a]	19 ± 6[a]	13 ± 8[a]

The bias is given as invasive minus noninvasive pressure. Each cell is the average difference ± standard deviation (mm Hg) for one patient for the difference between ART and either OSC or FINA pressure; the FINA and ART pressures were derived from the analog waveform. Each column is sorted for increasing average difference. The entries for any row do not necessarily reflect the same patient.

[a] Significant single group t-test (null hypothesis: average pressure difference = 0) at $P < 0.05$ without a multiple-comparison adjustment.

surement devices (13–15). Although the analysis methods recommended by Bland and Altman are now required by some journals (15) and recommended by others (16), the use of comparison techniques rather than regression and correlation analysis to scrutinize new monitoring devices is still relatively unfamiliar to most readers.

This new method of assessment specifically focuses on the questions of the repeatability of values for each monitor and on the comparison between values of two monitors. Repeatability is assessed by a coefficient of repeatability interpreted as follows: for the difference between two measurements to be attributed to a real alteration in patient physiology, the pressure difference from one measurement to another should be greater than the coefficient of repeatability. The coefficient of repeatability should be sufficiently small to allow easy detection of changes. However, our experimental design focused on comparison of devices; it was decided to create data sets only every 5 min as it would be unreasonable and would not reflect actual clinical care to cycle the OSC device more frequently than every 5 min for long periods. An experimental design to investigate repeatability would have required more frequent measurements. No repeatability analysis is thus reported.

Comparison of devices explores whether a systematic offset or bias exists between two monitors and defines the limits of agreement for single measurements from each of the monitors. If the difference between this paired measurement lies within the range of the limits of agreement, then the values are considered indistinguishable. If blood pressure differences of the magnitude of the calculated limits of agreement are clinically unimportant and biologically irrelevant for pressure monitors, then the devices are interchangeable. Regression and correlation analysis between values for the two monitors are not used.

Table 3. Monitor Comparisons Reports

Reference	Device	Pressure	Bias	95% Range of limits of agreement
Smith et al. (5)	FINA	Mean	−0.8	−8.4 to 6.8
Kurki et al. (8)	FINA	Systolic	4.8	−12.5 to 22.2
	FINA	Mean	−0.3	−15.5 to 14.9
	FINA	Diastolic	−1.5	−13.5 to 10.1
Green et al. (18)	OSC	Systolic	1.1	−12.3 to 14.6
	OSC	Mean	−0.7	−13.5 to 12.1
	OSC	Diastolic	−3.2	−16.4 to 10.0
Nystrom et al. (19)	OSC	Systolic	−0.7	NA
	OSC	Diastolic	−13.6	NA
Loubser (20)	OSC	Systolic	18.9	NA
	OSC	Mean	−0.3	NA
	OSC	Diastolic	−6.3	NA
Gorback et al. (11)	FINA	Systolic	8.4	−8.8 to 25.6
	FINA	Mean	6.8	−6.6 to 20.2
	FINA	Diastolic	1.1	−12.9 to 15.1
	OSC	Systolic	8.8	−13.6 to 31.2
	OSC	Mean	1.8	−17.6 to 21.2
	OSC	Diastolic	−1.6	−19.4 to 16.2

NA, not available.
The bias is given as invasive minus noninvasive pressure. The limits of agreement are calculated from the bias and the standard deviation of the bias. The units of bias and limits of agreement are mm Hg.

Device Comparisons

Our comparisons do show some systematic differences in bias between devices, pressures, and data capture. These biases are generally small (only several millimeters of mercury) and of little consequence. There is no need to adjust noninvasive blood pressure values (either OSC or FINA) for these small biases. These biases also do not clearly favor either OSC or FINA readings. Whereas the systolic pressure bias is greater for FINA, the diastolic pressure bias is greater for OSC. As opposed to the suggestion of Kurki et al. (8), there is no difference in bias for peripheral vascular disorders.

Although the bias was small, the variability of the difference between individual values of two monitors was large. This variability is specified by the limits of agreement (Table 1); this also might be called the precision of comparison between devices. Note that this 95% range is much wider than the 95% confidence interval surrounding mean bias.

One must decide how wide the limits of agreement may be and still allow comfort in choosing to use the FINA device. Our study provided a rational choice by simultaneously studying OSC and FINA. As good clinical care is believed possible with the OSC monitor, its limits of agreement with ART are a model for the desirable limits of agreement between FINA and ART. In fact, precision for FINA tended to be better (smaller limits of agreement) than for OSC. With both devices, the variability was of the same magnitude.

Whereas previous reports have usually offered no repeatability analysis, some have provided estimates of bias (Table 3). Although these reports have not generally described the statistical model and the computational methods, some have included a listing of standard deviations that allow limits of agreement to be calculated. The size of the bias of these studies is similar to those observed in this study. Limits of agreement from these studies seem to be somewhat smaller than in our study. The limits of agreement will obviously depend on the statistical model used to calculate the standard deviations. Our results are also consistent with a recently published comparison of intraarterial pressure monitoring with four methods of indirect pressure measurement (automated OSC, auscultatory, return-to-flow, and flicker) not including the FINA method (17). They noted that none of the four indirect methods clearly offered a superior performance, and that all were subject to erratic intrasubject and intersubject errors of accuracy and precision.

Analysis of our data shows that the difference between radial artery pressure and FINA measurements is no larger than the difference between radial artery and OSC pressure measurements. The FINA provides beat-to-beat waveform and numerical pressure display making it a more versatile noninvasive monitor than the OSC blood pressure monitor. The analysis we have completed shows no significant difference between its use in patients with a condition affecting the peripheral vascular system and those without such a condition.

Appendix: Statistical Methods

If a new method value was denoted B_{ij} and a standard method value was denoted A_{ij}, then $A_{ij} - B_{ij}$ was the difference or disagreement between the methods for that data set. The mean of all $A_{ij} - B_{ij}$ values was the average difference, also called the bias or offset, of the new method from the standard method. The statistical significance of a nonzero bias and its 95% confidence interval were obtained by estimating the standard error of the $A_{ij} - B_{ij}$ values [mean of $A_{ij} - B_{ij} \pm 2$(standard error of $A_{ij} - B_{ij}$)]. The 95% range for the limits of agreement between machines for single measurements was obtained from the bias and the standard deviation of the $A_{ij} - B_{ij}$ values [mean of $A_{ij} - B_{ij} \pm 2$(standard deviation of $A_{ij} - B_{ij}$)]. The estimation of parameters (mean difference, standard error, and variances) used a random effects analysis of variance model with $y_{ij} = \mu + a_i + e_{ij}$, where y_{ij} = the individual differences $A_{ij} - B_{ij}$, μ = the mean bias of the $A_{ij} - B_{ij}$ values, a_i = the random effect of subjects, e_{ij} = random error, $i = 1, \ldots, g$ (the individual index), and $j = 1, \ldots, n_i$ (the determination index for the ith individual).

The effects on bias of the presence or absence of vascular disease, the choice of noninvasive monitor, digital versus waveform data, systolic versus mean versus diastolic pressure, and pressure level were estimated by a mixed-model analysis of covariance. The model equation was $y_{ijklm} = \mu + a_i + \beta_k + \tau_l + \lambda_m + \delta \cdot x_{ijklm} + e_{ijklm}$, where y_{ijklm} = the jth difference Aij − Bij for the ith individual with the kth disease state, the lth device, and the mth pressure; μ = the mean bias of the Aij − Bij values; a_j = the random effect of subjects; β_k = the fixed effect of disease; τ_l = the fixed effect of digital versus waveform data, λ_m = the fixed effect of systolic, mean, or diastolic pressures, δ = the regression coefficient of the covariate, x_{ijklm} = the average of each A_{ij}, B_{ij} pair $[(A_{ij} + B_{ij})/2]$, and e_{ijklm} = the random error.

A plot of the differences $(A_{ij} - B_{ij})$ against the mean $[(A_{ij} + B_{ij})/2]$ allowed a visual inspection of the scatter of individual differences from the mean bias and the dependency of individual differences on the mean value. Histograms were constructed indicating the frequency of measurement differences $(A_{ij} - B_{ij})$. Only the central part of the scatterplots and histograms are displayed.

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CASE REPORTS

Ethical Issues in Anesthesia: Management of the Do-Not-Resuscitate Patient

Randall L. Martin, MD, Betsy E. Soifer, MD, PhD, and Wendell C. Stevens, MD

Oregon Health Sciences University, Portland, Oregon

On the duties of the anesthesiologist as a physician, Bourne (1) states that "the patient is not a problem; he is a *person*—with a problem." Nowhere is our duty as physicians more important than when administering intraoperative care to patients near death. Estimates are that from 5% to 20% of hospitalized patients have "do-not-resuscitate" (DNR) status (2,3). The geriatric population, those 65 yr or older, comprise 11% of our population and represent the fastest growing segment in our society (4). In the near future, a large number of geriatric patients with DNR status may require operations. Therefore, as physicians, we must grapple with the medical/ethical issues involved in the complex decision-making process of caring for patients with DNR status undergoing anesthesia and surgery.

"Do-not-resuscitate" is a vague term and can be interpreted in a number of ways. Anesthesiologists need to consider not only their own personal interpretation of DNR status but also what DNR means to the patient. The following three case reports contain issues that are examples of some of the important aspects of preoperative planning and forethought required when caring for patients with DNR status.

Case 1

An 83-yr-old woman fell at home. She had many active medical problems and an established history of noncompliance with medical therapy. A hip fracture, dehydration, and right middle lobe pneumonia were diagnosed in the emergency room. She was admitted to the intensive care unit. The patient, family, and her physicians discussed issues about her poor prognosis and jointly decided that DNR status should be established. Later that day, the orthopedic surgeons were consulted, and they scheduled the patient for urgent open reduction and internal fixation of her right femoral neck fracture.

Four months before this admission, she was hospitalized for treatment of congestive heart failure during which echocardiographic studies showed a deterioration in her complex valvular heart disease (aortic valve stenosis with regurgitation and mitral valve stenosis with regurgitation). At discharge, digoxin, furosemide, nitrates, potassium supplementation, alphamethyldopa, clonidine, atropinic bronchodilator, and cimetidine were prescribed to improve her cardiac function, to treat hypertension and her reactive airway disease, to correct for mild chronic renal insufficiency, and to serve as prophylaxis against upper gastrointestinal bleeding. Her family said she continued to smoke cigarettes, help in the kitchen, and participate in family life between discharge and the current admission.

When evaluated by the anesthesiologist approximately 12 h after the current admission, she was alert and immobilized in Buck's traction. Radial artery and pulmonary artery thermistor catheters were in place. She was receiving supplemental O_2 (F_{IO_2} [inspired oxygen fraction], 0.50) via mist mask. Her physical examination was remarkable for stable vital signs, a IV/VI pansystolic murmur at the apex with radiation to the axilla, a III/VI harsh systolic murmur at the left ventricular outflow tract radiating to both carotids, end-expiratory wheezing with right basal rales, and +1 pretibial edema. Hemodynamic values at this time included blood pressure, 100–180/90–104 mm Hg; heart rate, 60–70 beats/min; central venous pressure, 4 mm Hg; pulmonary artery occlusion pressure, 12 mm Hg; and cardiac index, 2.5 $L \cdot min^{-1} \cdot m^{-2}$. Electrocardiogram was unchanged from that obtained 4 mo before the present hospital admission. Chest roentgenogram demonstrated a right middle lobe infiltrate, an enlarged cardiac silhouette with atrial enlargement, and appropriate pulmonary artery catheter placement. Laboratory studies were remarkable for an elevated white blood cell count with left shift and for expected mildly elevated blood urea nitrogen and creatinine measurements. Antibiotic ther-

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Accepted for publication April 3, 1991.

Address correspondence to Dr. Martin, Oregon Health Sciences University, 3181 Sam Jackson Park Road, Portland, OR 97201-3098.

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0003-2999/91/$3.50

apy for the pneumonia had been started. A chart note documented that the patient, her family, and the anesthesiologist discussed her increased anesthesia risk and said that her trachea would be intubated and her lungs would be ventilated without further indication of what additional resuscitative efforts might be made. She was scheduled for the next available, appropriate operating room. While waiting (for 2–3 h), her condition rapidly deteriorated with the development of pulmonary edema, ischemic myocardial changes on the electrocardiogram, and hypoxia that required tracheal intubation, supported ventilation, and the initiation of circulatory support with inotropic, vasodilator, and antiarrhythmic drugs. Pending cardiovascular stabilization, the case was postponed. A few hours passed with the patient becoming more stable when a new orthopedic surgical consultant arrived and demanded that she be taken to the operating room emergently for surgery, stating that without surgery death was imminent in a short time and that he would proceed without the anesthesiologist, using local anesthesia only. When an appropriate operating room became available a few hours later, a second anesthesiologist evaluated the patient and concluded that her cardiovascular status was reasonably stable. A chart note documented that a discussion between her family and physicians (including the orthopedic surgeon) occurred and included discussion that her risk of dying intraoperatively was increased. What additional resuscitation efforts would or would not be undertaken was not recorded in the chart. She underwent a primarily intravenous narcotic anesthetic (40 μg/kg fentanyl, O_2, vecuronium) with minimal hemodynamic instability and returned to the intensive care unit with her trachea intubated, controlled ventilation, and receiving the same cardioactive infusions. An epidural catheter was inserted intraoperatively and used postoperatively to administer fentanyl epidurally for pain control. Her further postoperative course was complicated by repeated episodes of congestive heart failure and sepsis, worsening renal failure, and persistent respiratory failure preventing her removal from mechanical ventilation. Five weeks postoperatively, she was returned to DNR status by her family and physicians; all but nutritional and ventilatory support were withdrawn, and she died on postoperative day 42.

Case 2

A 71-yr-old obese man sitting erect on a stretcher in moderate respiratory distress and receiving supplemental O_2 arrived in the operating room for unilateral extracapsular cataract extraction with posterior chamber intraocular lens implantation and iridectomy. The ophthalmologists planned to proceed with retrobulbar and facial nerve blocks and monitored anesthesia care with the patient supine. Resuscitation status was not documented in the chart.

Bilateral cataracts made this patient legally blind. Severe steroid-dependent, chronic obstructive pulmonary disease required chronic home O_2 use and therapy with oral theophylline, prednisone, and atropinic and β-sympathomimetic bronchodilators. He remained in moderate respiratory distress at rest and was confined to a wheelchair. Recent pulmonary function testing confirmed moderate restrictive and severe obstructive pulmonary dysfunction. Bilateral glaucoma required topical pilocarpine, epinephrine, and acetazolamide use. Systolic hypertension was controlled with clonidine, and chronic asymptomatic atrial arrhythmias were treated with quinidine.

The patient was an obese man who, while sitting erect, used his accessory muscles of respiration and interrupted his speech by taking a breath after about every third word. He stated that this was his usual state of health and that he required at least two pillows to sleep at night. His respiratory rate was 24–36 breaths/min, and his heart rate was 110 beats/min and was irregular. The remainder of his physical examination was remarkable for anisocoria, distended jugular veins, bilateral end-expiratory wheezing in all lung fields, and 2+ bilateral pedal and pretibial edema. Laboratory data were significant for an elevated total CO_2 level, a therapeutic blood level of theophylline, and arterial blood gas values while breathing 3 L of O_2 through a nasal cannula with a pHa of 7.42, a $Paco_2$ of 38 mm Hg, and a Pao_2 of 112 mm Hg.

A discussion of risks and benefits of anesthesia was conducted between the patient, anesthesiologist, and ophthalmologist. The patient was highly motivated to undergo the operation to be able to read, even if he died intraoperatively. All parties agreed to proceed, understanding that the patient's position would have to be modified from supine, that minimal sedation would be used, and that any sustained ventricular arrhythmias would be treated. With the patient in the 20° reverse Trendelenburg position, receiving O_2 through a nasal cannula at 5 L/min and having minimal sedation, the blocks and operation proceeded uneventfully. Frequent multifocal premature ventricular contractions and supraventricular beats were recorded, but no therapy was required. The patient had an uneventful postoperative hospital course and was discharged on the second postoperative day. Before his 14-day follow-up appointment with the ophthalmologist, he was admitted to a local hospital for congestive heart failure and for an exacerbation of his pulmonary disease. He died during that hospitalization 22 days after operation.

Case 3

A 60-yr-old man, comatose and ventilator-dependent since an in-hospital cardiopulmonary arrest, was scheduled for tracheostomy. The patient was admitted to the hospital for evaluation of a synchronous ventricular pacer dysfunction and congestive heart failure. Fifteen days before the planned tracheostomy, an exploration of the pacemaker pocket and replacement of the lead was performed uneventfully using local anesthesia. One day after this procedure, the patient was found breathless and pulseless. Although the patient was resuscitated, he sustained an inferior and lateral wall myocardial infarction complicated by additional dysrhythmias, congestive heart failure, and limited neurologic recovery (Glascow coma scale 4). The family and physicians subsequently designated this man DNR. This patient was stabilized hemodynamically using digoxin, furosemide, captopril, and potassium phosphate. Other medications included cimetidine infusion and adequate nutrition through an oral-duodenal feeding tube.

On the day he was scheduled for tracheostomy, the patient was comatose, withdrawing bilaterally only to deep pain. He was afebrile with stable vital signs. A nasal endotracheal tube was in situ; he had clear bilateral breath sounds and had ventilator assistance at a rate of 8 breaths/min and a tidal volume of 10 mg/kg at an $\mathrm{FIO_2}$ of 0.30. The remainder of his physical examination was unremarkable, as were routine laboratory and roentgenogram evaluations. The anesthesiologist contacted the patient's family to clarify the DNR status for the upcoming operation. A consensus was reached to treat all untoward events in the perioperative period. As such, the DNR status would be rescinded. Tracheostomy was performed uneventfully using local anesthesia with minimal intravenous sedation. Within the next 2 days, the patient was weaned from the ventilatory support and DNR was reestablished. On the fifth postoperative day, the patient was found pulseless and breathless. No resuscitation was initiated.

Discussion

The case of Karen Ann Quinlan in 1976 focused the public's attention to the futility of using advanced medical technology to maintain biological life. In the aftermath, DNR orders were developed to protect the dying patient's rights (autonomy) against medical intervention when death from intrinsic organ failure is inevitable (4,5). As our case examples demonstrate, many elderly patients with DNR status arrive in the operating room without clear discussion of the multiple ethical dilemmas involved. Despite extensive literature devoted to DNR orders on hospital wards, no standard has emerged for the patient designated DNR coming to the operating room (6). In fact, the complex issues involved have caused problems and confusion for all physicians and policy makers who care for these patients.

A patient's resuscitation status is an important preparation factor when planning intraoperative care, especially in critically ill patients. The three cases described were selected because of the range of clinical ethical dilemmas represented. We do not suggest that all aspects of the management plans were ideal, but the patients do represent situations that arise. The patient in case 1 was alert, but it is doubtful whether adequate discussion of resuscitation efforts was made. In case 2, the patient was informed of the most likely untoward event and a documented agreement about treatment was obtained. The patient in case 3 was unconscious, and discussion with family members was necessary.

The terminology used in DNR status lends itself to confusion. "Resuscitation" may be interpreted as performing cardiopulmonary resuscitation (CPR), intubation, initiation of vasoactive drugs, or may include other treatments (7). One definition of DNR is "no CPR." Medicolegally, it is important to broadly discuss all forms of treatment that may be interpreted as resuscitation because the definition has not been tested in court. Because CPR is performed routinely in the absence of a DNR order and because physicians frequently cannot offer their patients a choice between CPR and the DNR order (8), the decision to perform CPR is commonly made without the patient's involvement (9). Without informed discussion and consent, concerns about patient autonomy arise. Therefore, informed consent with specific discussion about possible resuscitation measures such as CPR, intubation, and vasoactive drugs should be conducted (as in cases 2 and 3) before the operation.

Although the doctrine of informed consent has been controversial since its inception in 1957, it is central to both legal and ethical regulation of American medicine (10). Often, informed consent about DNR status takes considerable discussion and time with the patient preoperatively. In trying to make the informational exchange more of a process than an event, it is important to adhere to specific ethical principles to keep from presenting patients with complex medical information that they cannot understand.

Because the DNR is an advanced directive that identifies a patient in the process of dying, special care must be given to ensure that the operative procedure will not unduly cause harm to the patient (maleficence). Fortunately most operations for patients with DNR designation are palliative in nature

Table 1. Informed Consent—Suggested Guideline

1. Cover perioperative concerns preoperatively before patient comes to the operating room.
2. Take time to make the informed consent more of a process than an event.
   A. Identify high-risk factors.
   B. Answer specific concerns.
3. Reassure patient.
   A. Review data about cardiopulmonary resuscitation including the intraoperative incidence (1:1,000–10,000) and the possibility of adverse outcome (1:40,000 ventilator-dependent or disabled).
   B. Differentiate extrinsic events from organ failure-related (intrinsic) events that might occur in the operating room.
4. Arrive at a mutual decision.
   A. About patient's desires of your responses to intrinsic, extrinsic, and iatrogenically caused life-threatening events.
   B. About the possibilities of adverse outcomes including prolonged dependency on high technology.
   C. Whether to suspend DNR orders.
5. Move DNR decision into the postoperative time frame.
   A. Write in the chart that "any adverse neurologic outcome or dependency on high technology such as ventilator support or vasopressor support be suspended 24–48 h postoperatively," if patient or designated proxy agrees preoperatively.
6. Document complete discussion in the patient's chart and discuss the plan with the surgical team.

DNR, do not resuscitate.

such as tracheostomies and Hickman catheter and gastrostomy placements. A discussion with the patient about specific problems extrinsic to underlying organ failure or likely iatrogenic events (e.g., hypotension after pentothal, bradycardia caused by vasovagal response to a peritoneal tug) is important before obtaining consent. Also, one must attempt to mutually agree (with the patient) on the specific resuscitation measures potentially required intraoperatively (Table 1).

The possibility of adverse outcomes must be discussed with the patient. Prolonged dependency on high technology is a common fear to address. The patient's desires about the use of this technology should be discussed so that a note can be written in the chart such as "Mr. Smith states that any dependency on life support such as ventilators or vasopressors be stopped 24–48 h postoperatively if full recovery is not likely."

The expected outcome of CPR should be discussed with DNR patients or with their families. A review of patients who have received CPR indicates that it may not be very effective in the majority of hospitalized patients on wards (11). Peatfield et al. (12) assessed the results of CPR in 1063 patients within a 10-year period and found that although the initial survival rate was 32%, only 8.7% of the patients survived to be discharged from the hospital. Blackhall (8) and Hershey and Fisher (13) report less than a 6% survival in some patient groups. In the hospital, salient univariant predictors of mortality after CPR include class III or VI congestive heart failure (92%), hypotension (blood pressure <100 mm Hg for at least 1 day before the arrest), renal failure, and pneumonia (14).

However, outcome from CPR in the operating room is markedly different than outcome from CPR on wards. Keenan and Boyan (15) reported that of 27 patients with cardiac arrests occurring intraoperatively, five died in the operating room and 22 recovered, but four patients suffered brain damage and eight died shortly thereafter. One patient with brain damage died 8 mo postoperatively, another patient 2 mo postoperatively, and the others with brain damage died within the first 2 wk postoperatively. Of the 12 who recovered without any dysfunction (44%), all but one were ASA physical status III-IV patients preoperatively. These data indicate that the outcome from CPR is effective about 50% of the time. Unfortunately, patients who survive intraoperative CPR have a possibility of disability or brain damage, and some may require long-term care and be ventilator-dependent (in Keenan's study, 4 patients in 163,240 or ~1:40,000).

The decision to rescind DNR status is an ethical one involving patient autonomy and the physician's sense of beneficence. Autonomy describes the patient's ethical right to make decisions regarding himself, his own body and mind, and indicates the freedom of choice in considering medical treatment (16). Unfortunately, only 22% of conscious, critically ill patients are involved in a decision to designate DNR status for themselves because their mental status deteriorates before DNR is considered (3). Beneficence, the goal of "doing good" or achieving good outcomes is a high priority for physicians. A common demonstration of beneficence in the operating room has been the attempt to reduce perioperative mortality and morbidity (17).

A decreasing mortality in the operating room has been a time-honored objective as is the ethic of preservation of life. However, the quality of life has become a more socially important objective of patients. Our patient management in the operating room must be aggressive and precise to continue to decrease perioperative mortality. Studies have shown that nurses decrease the aggressiveness of their intervention when caring for a DNR patient (Table 2) (18). Intraoperative management of the patient with DNR orders may be so suboptimal as to cause death and may be legally misinterpreted as intentional killing or active euthanasia, therefore subjecting the

Table 2. Aggressiveness of Nursing Care for Patients Designated DNR

Conditions	No DNR (%)	With DNR (%)
Admission to ICU	47	28
Needs aggressive care	69	37
Restart IV	77	63
Replace NG tube	54	31
Begin TPN	62	39
Neuro checks every 2 h	85	59
Vital signs every 2 h	68	30
Chest physiotherapy every 2 h	70	55

DNR, do not resuscitate; ICU, intensive care unit; IV, intravenous; NG, nasogastric; TPN, total parenteral nutrition.

Based upon data from Reference 18.

anesthesiologist to medicolegal dilemmas (15–17,19–22).

At the time case 3 occurred, the hospital staff was developing an operating room policy about DNR status and has subsequently decided to rescind the DNR status during perioperative care and PACU recovery. This gives the anesthesiologist the freedom to respond to ongoing clinical events due to intrinsic organ failure and to extrinsic mishaps such as drug reactions and equipment malfunction. If it is impossible to rescind orders uniformly, one should discuss at length the informed consent with the patient. When the physician uses these suggested steps as guidelines during the informed consent process, most patients will agree to rescind their DNR order.

If patients do not agree to rescind DNR orders, it may be appropriate to obtain consultation from a hospital ethics committee such as the one modeled at the Massachusetts General Hospital (23). Certainly all factors that promote good ethical decisions should be sought, such as (a) reliable data, (b) open communication, (c) optimal informed consent, (d) advanced planning, and (e) multidisciplinary input. A reasonable plan for the patient with an ambiguous resuscitation status is to require a written note from the attending physician that explains the patient's DNR status, what DNR means, documentation of informed consent in the progress notes, and discussion of intraoperative DNR status and care. This is helpful to the patient, to the other health care professionals who participate intraoperatively, and to the anesthesiologist.

The authors hope that this manuscript will stimulate much needed discussion regarding how best to manage care for the dying patient designated DNR admitted for surgery.

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Spinal Anesthesia Using Subcutaneously Implanted Pumps for Intrathecal Drug Infusion

Dennis W. Coombs, MD and Nora Fine, MD

Pain Management Service, Department of Anesthesiology, Dartmouth Hitchcock Medical Center,
Hanover, New Hampshire

Indwelling intrathecal and epidural infusion pumps are increasingly prevalent in chronic pain treatment, for spinal infusion based treatment of spasticity from spinal cord injury and multiple sclerosis, and as an avenue for drug research into spinal cord diseases like amyotrophic lateral sclerosis (1–6). For surgical anesthesia in patients with such implanted systems, spinal or epidural anesthesia often may be preferred. However, the preexisting spinal catheters and related hardware present both anesthetic hazards and opportunities. If spinal or epidural anesthesia is contemplated, the location and integrity of the indwelling catheter must be considered. Yet, the exact position of the spinal catheter entry into the spinal canal is often not precisely known, leading to confusion over the safest level for needle insertion. Furthermore, there is a risk of puncture or actual severance of the catheter along its length either internal or external to the spinal canal. Such catheter damage may result in unrecognized failure of drug infusion. The clinical consequence will be the return of pain, spasticity, or loss of the original action desired from the infusion of the spinal drug. Serious rebound or abstinence problems may be precipitated.

If the spinal catheter damage is recognized, a diagnostic process should be done to determine the location of the catheter defect. This may entail radiographs, diagnostic blocks, or radiologic contrast dye studies with attendant extra costs and medicolegal and clinical risks. Fortunately, several of the implantable infusion pumps and all the implantable injection reservoirs or ports permit auxiliary injection over and above their continuous infusion mode. We have frequently encountered patients with implanted intrathecal catheters and subcutaneous delivery pumps who require anesthesia. In this retrospective report, we present the management of three such patients in whom we elected to proceed with regional anesthesia through the auxiliary injection system of their implanted pump. This experience was accumulated during a study of spinal narcotic analgesia sponsored by the National Institutes of Health and during an independent study of spasticity treated by intrathecally administered drugs approved by Dartmouth's Committee for the Protection of Human Subjects with written informed consent from the participants (patient 3 was not part of these protocols but was treated based on this experience). Spinal anesthetics were successfully administered through their indwelling intrathecal catheters, thus decreasing discomfort and risk of spinal headache, bleeding, and infection, while naturally avoiding potential injury to the implanted system by performance of a percutaneous lumbar puncture.

Method

We have predominantly used two types of implantable drug delivery systems at this institution: the Infusaid model 400 with auxiliary side port injection attachment (Shiley Infusaid, Norwood, Mass.) and the Therex Implantable Drug Pump, model 3000, with a single central septum (Therex, Walpole, Mass.). The cutaways shown in Figures 1 and 2 illustrate the procedure whereby the bolus features of these pumps are used. The Infusaid Auxiliary Sideport (Figure 1) is accessed through a 22-gauge Huber noncoring needle. The Therex port is also accessed with a standard 22-gauge Huber needle to refill or empty the pump (Figure 2A). An interesting feature of the Therex device is a two-story set of chambers lying beneath the central septum (Figure 2A, B). The first is a bolus injection port in which the floor is a septum forming the roof of the second chamber—the recharge or refill chamber. Therefore, bolus injection requires a separate special bolus auxiliary needle to access the bolus injection port. This special-access

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Supported in part by grants from the U.S. Public Health Service (CA33865); the National Cancer Institute; the Robert J. Osgood, Jr., Memorial Fund; Therex Corporation, Walpole, Massachusetts; and the William L. Garth, MD, endowment at Dartmouth (D.W.C.).

Accepted for publication April 12, 1991.

Address correspondence to Dr. Coombs, Pain Management Services, Dartmouth Hitchcock Medical Center, Hanover, New Hampshire 03755.

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0003-2999/91/$3.50

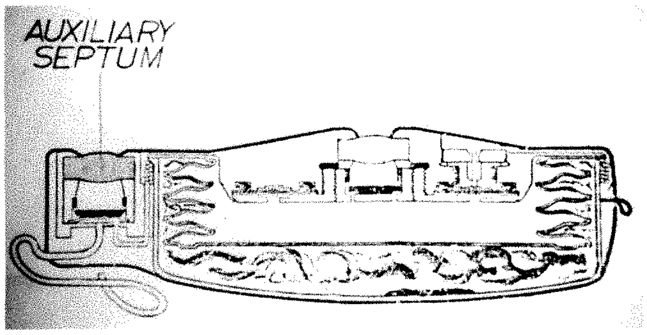

Figure 1. Cutaway view of the Shiley Infusaid model 400 implantable drug pump. Note the central drug access septum, innermost drug chamber within an expandable metal bellows, and the outermost fluorocarbon chamber. The auxiliary septum (left side of the device), used for spinal anesthetic injection in this report, provides access to a small port chamber located astride the end of the capillary restriction system that controls the drug flow rate of the pump; the auxiliary port is thus an extension on the main body of the pump (photo courtesy of Shiley Infusaid Corp., Norwood, Mass.).

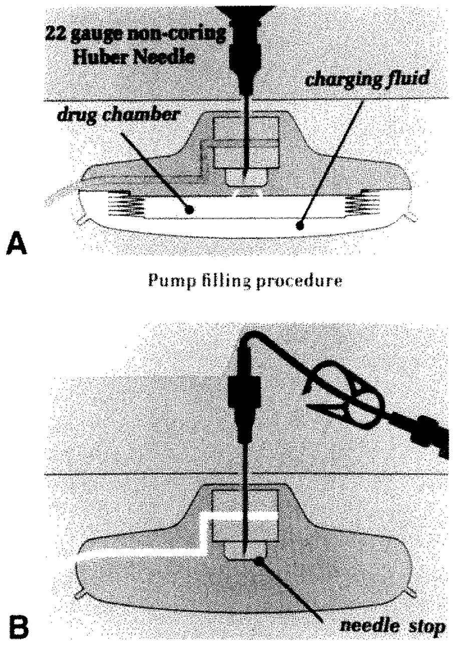

Figure 2. **A.** Cutaway of the Therex model 3000 Implantable Drug Pump, with dual-septum central access. This panel shows a 22-gauge Huber needle inserted through both septa to abut the needle stop with drug exiting into an expandable inner metal bellows drug chamber. A second outer chamber surrounds the metal bellows and contains a fluorocarbon charging fluid as in the Infusaid-type continuous flow pump in Figure 1. **B.** Therex special bolus injection needle again inserted to abut the internal needle stop. The blank portion of the needle extends into the second lower septum, whereas the side hole of the special bolus needle permits the bolus drug to be injected into a small port between the two central septa. The white line extending to the left shows the pathway of bolus drug exit through the pump's external catheter (photo courtesy of Therex Corp., Walpole, Mass.).

needle has a solid-steel wire blank with Huber-type point extending beyond standard hypodermic tubing. A side hole is positioned in the tubing above the blank portion of the needle that projects into the refill chamber when abutting the needle stop (Figure 2B). The side hole then opens into the auxiliary bolus chamber to prevent injection into the refill chamber and to permit access to the bolus port. The authors have used the following approach to conduct spinal anesthesia through the implanted pumps.

First, the patient is prepared with monitors and with intravenous access followed by standard preparation and drape with strict attention to asepsis. The following are readied on a sterile tray: a sterile three-way stopcock, sterile pump access needles, a 10-mL sterile syringe with 10 mL of preservative-free saline solution for flushing the spinal anesthetic (approximately 0.5 mL of dead space can be assumed with the implanted pump auxiliary port systems), and a 2-mL syringe for drawing and injecting the spinal anesthetic. The choice of anesthetic will obviously vary with the length of the anticipated procedure. If the anesthesiologist needs to be draped away from the procedure, a suitable length of low-volume access tubing can be interposed between the pump and the stopcock injection system.

The patient is positioned on an appropriate table to permit the adjustment of the sensory level depending on the baricity of the local anesthetic to be used. A skin wheal is raised with local anesthetic injected over the port site. The stopcock, an extension line if one is to be used, and prefilled syringes should be assembled; and the needle and stopcock to be used should be cleared of air. This is done to prevent intrathecal injection of an air embolus with resultant pneumoencephalogram and related headache. The auxiliary port is accessed by inserting the Huber needle or Therex access needle (depending on the type of pump) through the septum. If possible, the distal part of the intrathecal line is aspirated to remove any drug in line to avoid a hazardous bolus. The calculated dose of spinal anesthetic is then injected. We routinely flush with 2 mL of preservative-free saline solution both to clear the intrathecal catheter of any hyperbaric glucose (if used) and to ensure that all the anesthetic reaches the intrathecal space on time. The patient is then observed for hemodynamic effects, and the sensory level is determined to check whether further drug is needed.

After completion of the anesthetic administration, any remnant of the intrathecal saline solution in the spinal catheter should be cleared by reloading with the appropriate concentration of spinal drug previously delivered by the device. This maneuver is intended to avoid precipitating withdrawal by an interruption in drug therapy. If the anesthetic procedure is particularly prolonged, at least a partial dose

Table 1. Summary of Clinical Details

Patient No.	Surgical procedure	Anesthetic	Dose (mg)	Peak level	Results	Recovery	Notes[a]
1	Cystoscopy, change suprapubic tube	Bupivacaine hyperbaric	7.5	None	No block	3 h	1
1	Dimethyl sulfoxide instillation, cystoscopy	Bupivacaine hyperbaric	4	T-10(r) T-12(l) partial motor	Effective block	2 h 55 min	2
1	Removal of urethral catheter, reinsertion of suprapubic tube with bladder irrigation	Lidocaine hyperbaric	40	T-4 block	Effective	55 min	
1	Reinsertion of suprapubic tube with bladder irrigations	Lidocaine	40	T-4 block	Effective	1 h 15 min	
1	Reinsertion of suprapubic tube with bladder irrigations	Lidocaine hyperbaric	30	T-8 block	Effective	2 h	3
1	Reinsertion of suprapubic tube, examination of abdomen and tract	Lidocaine	35	T4-6 block	Effective	2 h 15 min	
1	Reinsertion of suprapubic tube with bladder irrigations	Procaine	30	T-8 block	Effective	None	
1	Reinsertion of suprapubic tube with bladder irrigations	Procaine	70	T-8(l) T-9(r) block	Effective	None	4
2	Infusaid pump replacement	Lidocaine	20	T2-4?[b] block	Effective	2 h 25 min	4
3	Sciatic nerve port implantation	Bupivacaine hyperbaric	7.5	T-7 block	Effective	4 h 25 min	
3	Removal of sciatic nerve port	Lidocaine hypobaric	50	T6-8 block	Effective	38 h 5 min	

r = right, l = left highest sensory level detected.

[a] 1, 500-μg intrathecal morphine after block for postsuprapubic tube bladder spasm; 2, 75-μg intrathecal fentanyl after block; 3, 20-mg ephedrine to treat hypotension; 4, 100-μg intrathecal fentanyl after block.

[b] C5-6 quadriplegic with partial sensory level T2-4.

might be given to reestablish the steady-state spinal fluid levels that constitute maintenance therapy. The risks of significant breakthrough symptoms, precipitation of a spinal abstinence syndrome particularly in antispasticity therapy, and even mass reflexes with late bladder distention should be appraised.

Table 1 contains a synopsis of important details for all three patients. These capsule clinical histories emphasize the potentially complex clinical presentations of patients treated with implanted pumps and the innovative use of such pumps to deliver spinal anesthesia.

Case Reports

Patient 1

A 36-yr-old man with acquired immune deficiency syndrome had a Therex model 3000 infusion subcutaneous pump and an L4-5 intrathecal catheter placed for relief of incapacitating bladder pain and spasms and of burning leg pain secondary to AIDS-associated interstitial cystitis and peripheral neuropathy, respectively. An intrathecal morphine test dose (1 mg) had completely eliminated his spasms and pain for more than 24 h. Intrathecal morphine therapy through this pump has gradually escalated within 22 mo from the starting dose of 1 mg/day to his current regimen of 25 mg/mL of Duramorph with 0.75% bupivacaine at a rate of 1.7 mL/day. Chronic care has been complicated by multiple suprapubic catheter obstructions necessitating urodynamic studies, catheter changes, irrigations, reanchoring, and revisions of the suprapubic tract. Each procedure resulted in temporary recurrence of the painful bladder spasms for periods of 6-24 h. He has required anesthesia and analgesia eight times (seven successfully) for these various urologic procedures; coexistent with each event was clinically significant anemia (down to HBG 6.5 at times) and low leukocyte count (600-1500 granulocytes) and T_4 cell counts in conjunction with chronic AZT, inhaled pentamadine prophylaxis, and most recently guancyclovir. To facilitate these procedures, a subarachnoid block has been used eight times (seven successfully) via the indwelling pump catheter and the implanted pump. The second spinal anesthetic failed because the anesthesia team involved was technically unfamiliar with the implanted system; the anesthesia team used general anesthesia instead. A bolus of intrathecal fentanyl was also added at the end of most of these urologic procedures to block the increased intensity of the patient's bladder spasms seen after bladder manipulation. The patient is then sent home with a syringe containing 250 μg of fentanyl attached to the described three-way system, and he self-administers 1 mL every 3–4 h for any breakthrough spasms. This has allowed him to return home (2-h drive) an hour or so after the procedure.

Patient 2

A 34-yr-old man, a C-6 quadriplegic with severe spasticity, had an Infusaid model 400 pump placed subcutaneously with the intrathecal catheter tip at T12-L1 after it was demonstrated successfully that spinally administered morphine would ablate his flexor spasms. In 10 yr of using continuous spinal drug delivery, we have had two pump failures by stoppage, including this case. Approximately 6 wk after pump implantation, he was admitted with severe headaches and a feeling of impending doom. He had been subject to autonomic mass reflexes with constipation, disimpactions, and bladder distention. He and his spouse had treated these with emergency injections of chlorpromazine. His arterial blood pressure on emergency room admission was widely gyrating and reached 260/150 mm Hg at times. An intravenous catheter was placed, and intravenous chlorpromazine was given to decrease his arterial pressure. A roentgenogram with soluble contrast dye injected through the implanted pump auxiliary port confirmed that his intrathecal catheter was still in place and not obstructed. A high residual volume in his pump was indicative of a serious slowdown or stoppage. The malfunctioning pump was replaced with another Infusaid model 400 under subarachnoid block administered through the failed indwelling pump via the sideport. The replacement Infusaid device infused intrathecal preservative-free morphine on an average of 2.6 mL/day. The dose has gradually increased from 0.5 to 1.7 mg/day. With control of his flexor spasms, he has continued to work part-time despite his quadriplegic condition.

Patient 3

A 60-yr-old, insulin-dependent diabetic man with serious peripheral vasculopathy and diabetic neuralgia, was admitted with a history of chronic pain in his right above-knee, amputation stump. Sciatic nerve explorations had been performed for neuroma without control of his pain. Several years earlier at another institution, an Infusaid model 400 had been implanted with an intrathecal catheter at L1-2. This procedure and the earlier treatment were performed to treat the phantom limb pain in his amputated right leg. The pump was infusing morphine sulfate at 9 mg/day without adequate relief. Although he stated that initially the phantom pain had responded to the intrathecal morphine, his sciatic pain had never been controlled. Two separate sciatic nerve injections with local anesthetic blocked the leg pain completely. He refused reexploration of the nerve. The problem of sustaining an effective block was resolved by implanting an innovative custom catheter tunneled from his sciatic nerve to a subcutaneous location on his lower chest wall. This was accomplished under bupivacaine spinal anesthesia given through his implanted pump. He successfully treated himself through the port by injecting 5 mL of initially 0.5% and eventually 0.75% bupivacaine every 5–6 h to relieve his pain. One week before a scheduled revision of his sciatic system, an infection developed involving the sciatic nerve port site and catheter. The system was successfully removed under a spinal anesthetic administered through the indwelling intrathecal pump via the sideport. Unfortunately, the spinal anesthetic precipitated recurrence of a painful phantom limb pain syndrome with burning and aching sensations in the amputated toes and foot of his right leg (7). This was in turn treated with intrathecal fentanyl through the implanted pump (8). Lancinating pain in the sciatic nerve required a lidocaine infusion for 36 h and subsided partially on an oral mexiletine regimen after several weeks. He recovered well and is awaiting reimplantation of another pain relief system.

Discussion

These three patients reflect very unusual case presentations emanating from three different applications of spinal drug infusion: cancer-related pain in an AIDS patient manifesting as bladder spasticity (details are reviewed much more extensively in another publication [9]), intractable flexor spasms in a C-6 quadriplegic patient, and diabetic neuropathy and postamputation phantom limb. The latter indication and the case report presented are clearly controversial. Although the treatment of cancer pain with chronic spinal narcotics is well accepted, the extension of this therapy to nonmalignant pain is more problematic, in part owing to greater patient longevity, to tolerance that develops to the spinal analgesics, and to basic inadequacies in our understanding of the spinal substrates modulating such central pain states (10).

Primarily, these three cases illustrate the functional utility of an indwelling intrathecal access system to achieve effective spinal anesthesia, spinal narcotic analgesia, and blockade of spinal mass reflexes in high spinal injury patients. This approach requires a rudimentary understanding of the spinal technology available, a reasonable technique to permit safe intrathecal access per the implanted systems, and finally an appreciation for some attendant physiologic processes. We have long used the bolus functions of these implanted pumps for a variety of reasons: to deliver probe doses of narcotics for estimating tolerance and correct doses, to initiate a new spinal drug, to obtain spinal fluid samples for diagnostic testing or for estimating steady-state drug levels in the cerebrospinal fluid, to inject diagnostic radiologic contrast dyes for determining the integrity of implanted systems and patency of the cerebrospinal fluid column when spinal cord compression is considered. The utility of an easily accessed spinal system for spinal anesthesia is obvious.

The monitoring issues, preparation, and positioning for spinal anesthesia through an implanted pump are little different than if performed through a percutaneous needle. As no needle is inserted, there should be no risk of either direct needle injury or spinal headache, assuming that air is not accidentally injected. Preparations to avoid this complication have already been discussed. Some factors are clearly different compared with percutaneous spinal anesthesia. The position of the spinal catheter tip is unknown. Some clinicians actually attempt to place the catheter at the dermatomal center of the pain syndrome; thus, at times, the catheters may actually overlie the thoracic spinal cord. Considerations such as dose and positioning might clearly be affected by this knowledge. Alternatively, an adequate and safe block might be achieved simply with slow local anesthetic titration.

The exact dead volume of the pump bolus injection port and spinal catheter will not be available. Thus, a flush system is needed to ensure complete delivery of all the chosen local anesthetic. Some barbotage may be unavoidable therefore. It is important that the injection rate and flush be slow to avoid excessive barbotage and potential pressure-induced neural injury or inadvertently high spinal anesthetics. A flush is also indicated if a viscous dextrose solution is to be used to make the solution hyperbaric. Experience with viscous radiologic contrast injection through these systems points to the need to clear such sticky solutions before they occlude a very expensive system and precipitate a costly surgical correction.

The content of the catheter leaving the pump is a concern both at the initiation of the procedure and at its termination. The potential for a period of inadequate drug delivery after a bolus of local anesthetic and even precipitation of abstinence was addressed earlier. In contrast, at the start of spinal anesthetic administration, if the auxiliary system and its intrathecal catheter cannot be aspirated to clear some of the drug in the bolus pathway, a significant bolus of the solution coming from the pump may be delivered. This potential downside of bolus injection through any of these systems is perhaps most pertinent to pump-delivered drugs such as baclofen. An accidental bolus injection of even 1 mL of the pump solution in the catheter and the port pathway might contain a quantity of the agent capable of causing serious respiratory depression (e.g., morphine) or profound muscle paralysis (e.g., baclofen). A significant degree of narcotic tolerance in the case of morphine infusion may protect the patient, but caution is clearly advised. Baclofen tolerance has been much less evident, and patients receiving this spinal therapy often have decreased respiratory reserve, e.g., quadriplegia. Clearly, the need for monitoring for a significant time may make a more conventional technique more attractive if the intrathecal system cannot be adequately aspirated at the time of the spinal local anesthetic injection.

A peculiar situation is created when subarachnoid local anesthetic injection is to be given through a pump system through which the patient is already receiving continuously both intrathecal narcotics and local anesthetics, as in patient 1. The extent of potential drug synergism or the degree of chronic local anesthetic tachyphylaxis was not predictable. Fortunately, relatively small amounts of the short-acting local anesthetic procaine were well tolerated. This local anesthetic option, when coupled with the anesthesiologist's capacity to repetitively redose through the system, further underscores the advantages of the transpump approach under the potentially complicated anesthetic conditions that may be encountered.

Several prominent features of patients 2 and 3 deserve passing attention. Specifically, serious side effects were associated with stoppage of intrathecal morphine infusion in patient 2 and the use of spinal anesthesia in patient 3. Indeed, patient 2, a severe spastic quadriplegic, was admitted with essentially continuous and near fatal spinal autonomic mass reflexes owing to pump failure and to the related loss of intrathecal morphine delivery. This was ultimately controlled again through the pump auxiliary sideport. An external pump was used to deliver intrathecal morphine until the pump was replaced under spinal anesthesia. Parenthetically, we have similarly used an external pump to percutaneously titrate the switch from intrathecal pump-delivered morphine to baclofen to improve control of spasticity associated with multiple sclerosis.

In patient 3, we triggered a difficult recurrence of phantom pain syndrome during otherwise successful spinal anesthesia (7). Obviously, the intrathecal morphine infusion dose was insufficient to block this phenomenon of apparent central origin. Knowledge that intrathecal fentanyl will break the acute attack is useful (8). The latter had little effect, however, on the neuropathic pain patient 3 experienced in his sciatic stump. We were successful in controlling the latter symptoms with 3–4 mg/min of intravenous lidocaine infusion followed by substitution of orally administered mexiletine.

In summary, we have reviewed the novel delivery of spinal anesthesia through the optional bolus port systems of implanted pumps in patients receiving chronic intrathecal drugs. The anesthesiologist should consider this valuable technique when such patients are admitted for operation. However, due caution must be exercised for the complex issues that regional anesthetic management of such patients will entail.

The authors thank Larry Jensen, RN, Karen Vernier, RN, and Richard L. Saunders, MD, for participating enthusiastically and effectively in the care of these patients; Sue Hazelton, PharmD, for preparing the continuous spinal drugs used; Therex Corp., Walpole, Massachusetts, for providing the Therex model 3000 device used in one patient; and the A.H. Robins Co. for graciously providing the concentrated preservative-free morphine sulfate, Duramorph, used in these patients.

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Letters to the Editor

Prevention of Nitrous Oxide-Induced Increases in Endotracheal Tube Cuff Pressure

To the Editor:

I read with interest the letter by Brandt (1) in the February edition of your journal. I wish to propose an even simpler method of preventing excessive rise in endotracheal tube cuff pressure during the administration of a nitrous oxide anesthetic. If one simply fills the endotracheal tube cuff with the mixture of nitrous oxide and oxygen to be used during anesthesia administration, then there is no diffusion gradient by which nitrous oxide can enter the cuff. There will therefore effectively be no change in cuff pressure during anesthesia. This simple system is remarkably effective.

Paul Morgan, FCAnaes
Sir Humphrey Davy Department of Anaesthesia
Bristol Royal Infirmary
Marlborough Street
Bristol, BS2 8HW, United Kingdom

References

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Back Pain in Volunteers After Epidural Anesthesia With Chloroprocaine

To the Editor:

I found the recent report by Hynson et al. (1) very interesting. I frequently use 2% and 3% 2-chloroprocaine in my practice while performing diagnostic and therapeutic anesthetic blocks for patients in chronic pain.

I also have seen severe back pain and muscle spasm after these blocks but my experience would not implicate ethylenediaminetetraacetic (NaEDTA) acid as the precipitating agent of this phenomenon as was suggested. I frequently use 2% 2-chloroprocaine in performing my blocks and only rarely have a problem despite the use of relatively large volumes (20–60 mL injected in approximately 5-mL increments), whereas on the few occasions I have needed to progress to 3% 2-chloroprocaine, there seems to be a high incidence of muscle spasm and severe pain as the block wears off—despite the use of smaller volumes overall. As NaEDTA is present in both formulations in the same concentration, based on my own experience it is unlikely that it is the sole source of this phenomenon. However, I agree it is a real phenomenon and something seen only rarely with the previous formulation of this drug.

Franklin J. Day, MD
Pain Relief Center
112 LaCasa Via, Suite 220
Walnut Creek, CA 94598-3004

Reference

1. Hynson JM, Sessler DI, Glosten B. Back pain in volunteers after anesthesia with chloroprocaine. Anesth Analg 1991;72:253–6.

In Response:

In our discussion, we suggested several potential etiologies for back pain after epidural chloroprocaine administration, but did not endorse one in particular. The possible causes listed included the theory proposed by Fibuch and Opper (1) that pain is caused by EDTA. In support of this etiology, Wang et al. recently reported that hourly lumbar epidural injections of 0.1 mL of 0.1% EDTA in rats result in tetanic contractions of the lower extremities and focal neuropathologic changes when the total dose exceeded 0.1 mg (2). For comparison, the total dose of disodium EDTA after a 35-mL lumbar epidural injection of Nesacaine-MPF in humans would be 3.5 mg. (The concentration of disodium EDTA in Nesacaine-MPF is 0.011%.) Although not definitely implicating EDTA as the causative agent, this study suggests that further investigation of its neurophysiologic effects, neurotoxicity, and myotoxicity is warranted.

Dr. Day's personal observations of back pain after the use of chloroprocaine in the pain clinic are interesting. One consistency in the published reports, as well as the experience of Dr. Day and other clinicians with whom we have spoken, is that this characteristic back pain after 3% chloroprocaine has been observed primarily in patients treated on an outpatient basis. The recent emergence of this problem could in fact be unrelated to the introduction of Nesacaine-MPF. Rather, the increased number of outpatients receiving epidural blocks in recent years may simply have helped to uncover the association of back pain with epidural chloroprocaine.

James M. Hynson, MD
Daniel I. Sessler, MD
Department of Anesthesia
University of California, San Francisco
San Francisco, CA 94143-0648

References

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Sensitivity and Specificity of Tests of Malignant Hyperthermia Susceptibility

To the Editor:

Dr. Olgin and colleagues (1) are to be commended for developing a noninvasive test to detect malignant hyperthermia susceptibility. They report estimates of the sensitivity and specificity of the new test as 98.8% ± 11.8% and 95.3% ± 20.3%, respectively. In their discussion, they concede that "the specificity of the NMR test may be as low as 75% (95.3% ± 20.3%) . . ." but neglect to mention the opposite extreme of the range. As the sensitivity and specificity of a test cannot be greater than 100%, the reported results and ranges, presumably mean and standard deviation, do not make sense. These results and the methods used to derive these estimates need to be clarified further.

Thomas Hackmann, MD, FRCPC
Department of Anaesthesia
University of Alberta Hospitals
WMC 3B2.32
8440—112 Street
Edmonton, Alberta
T6G 2B7 Canada

Reference

1. Olgin J, Rosenberg H, Allen G, Seestedt R, Chance B. A blinded comparison of noninvasive, in vivo phosphorus nuclear magnetic resonance spectroscopy and the in vitro halothane/caffeine contracture test in the evaluation of malignant hyperthermia susceptibility. Anesth Analg 1991;72:36-47.

In Response:

Dr. Hackmann appropriately questions the values of sensitivity and specificity given in our publication (1). Deriving a true value for these parameters is difficult when an absolutely true diagnosis is not known. One can only compare with the results of an existing diagnostic test. Because we compared the NMR test with another diagnostic test, statistical methods were needed to estimate these values, which produced a sample mean and standard deviation. These were expressed in terms of confidence intervals.

A confidence interval is merely an expression of uncertainty that gives a range, assuming a certain probability, to a particular *sample* mean that estimates the *population* mean, taking into account sampling errors. The range is based on an estimation of sampling errors (the standard deviation) and a chosen probability (e.g., 95%, 99%) and *not* on possible real values for the population mean. The population mean is not a random variable. The confidence interval merely estimates the range around a sample mean in which the population mean falls with a given probability, taking into account sampling errors.

The following is an example to illustrate this, using simple "made-up" poll data. Suppose we asked five anesthesiologists what percentage of this journal they read and the responses were as follows:

1. 40%
2. 96%
3. 20%
4. 98%
5. 100%

The mean response is 70.8% with a standard deviation of 33.9%. This would result in an interval of 70.8% ± 33.9% (mean ± SD), which would make one extreme of the interval 104.7%—clearly an impossibility.

In our published study, we used the methods of Gart and Buck to estimate the true sensitivity and specificity of our test. The intervals merely give the range within which the true values are likely to fall. As Dr. Hackmann states, the sensitivity and specificity of a test cannot be greater than 100%. Although the confidence interval of our estimated specificity is 95.3% ± 20.3%, the true specificity probably lies between 75% and 100%.

Jeffrey Olgin, MD
Department of Medicine
University of California, San Francisco
San Francisco, CA 94143

Henry Rosenberg, MD
Department of Anesthesiology
Hahnemann University Hospital
Philadelphia, PA

Reference

1. Olgin J, Rosenberg H, Allen G, Seestedt R, Chance B. A blinded comparison of noninvasive, in vivo phosphorus nuclear magnetic resonance spectroscopy and the in vitro halothane/caffeine contracture test in the evaluation of malignant hyperthermia susceptibility. Anesth Analg 1991;72:36-47.

Map of Contributions to *Anesthesiology* and *Anesthesia and Analgesia*

To the Editor:

The accompanying map illustrates the percentage share of scientific papers published in two main anesthesiology journals in 1990: *Anesthesiology* and *Anesthesia and Analgesia*. Only clinical and laboratory investigations were taken into account (editorials, reviews, case reports, and medical intelligence articles were excluded). Percentage shares for each state were determined from the numbers of papers produced by authors from each state in 12 monthly issues (January through December) of both journals. A similarly constructed map for the year 1965 appears in the inset.

In 1990, California ranked first (62 articles); Pennsylvania, second (22 articles); and Minnesota, third (18 articles). These numbers are mostly a reflection of academic activity in large anesthesiology departments.

The comparison of the 1990 map with that of 1965 indicates that the greatest improvement was made by North Carolina (from 0% to a 5.1% share). The states that have increased their share of publications by a factor of two to three are Washington, Wisconsin, Alabama, Connecticut, Iowa, and Minnesota. New York's share decreased from 22.6% (first place in 1965) to 4.7%. The map

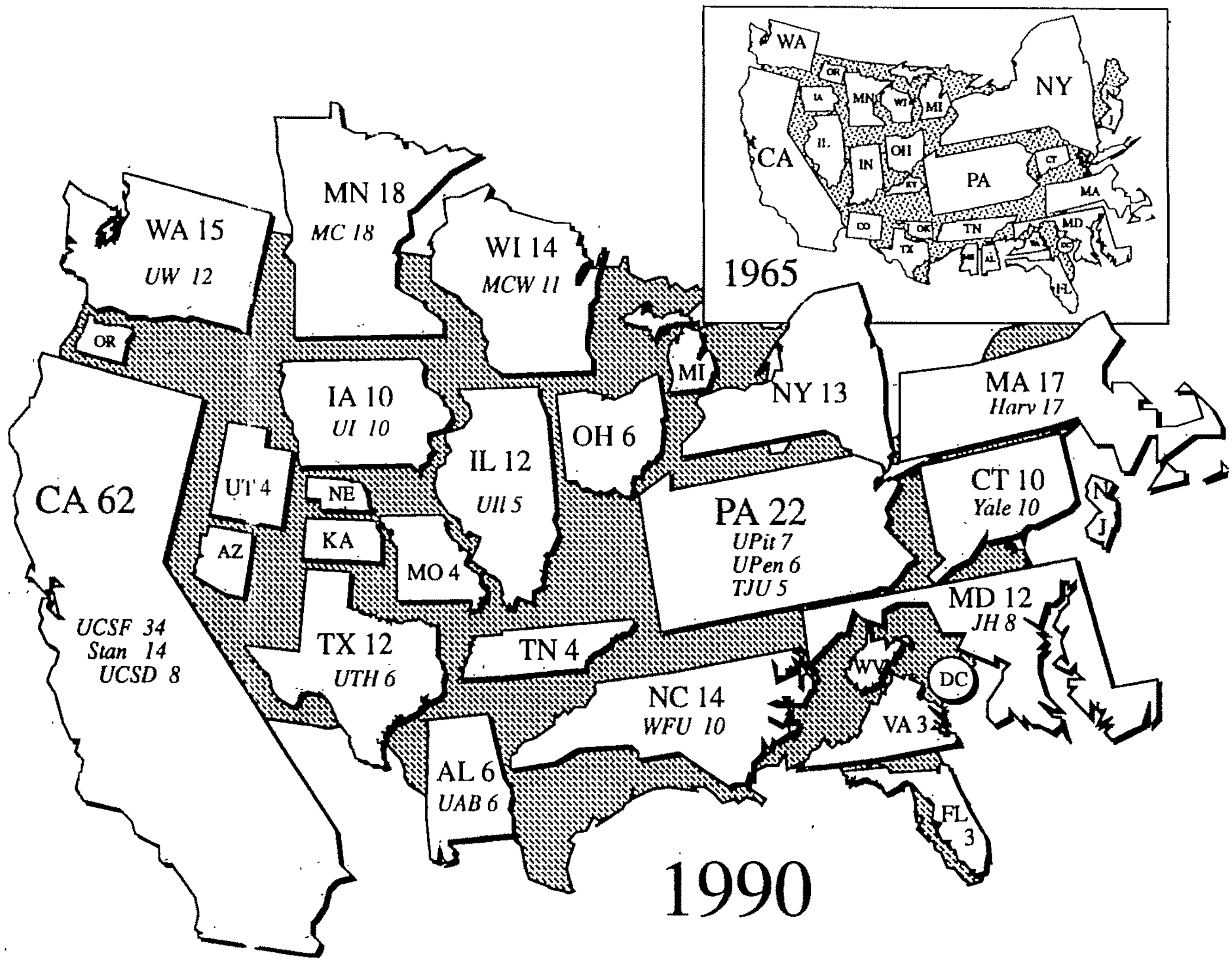

Figure 1. Publications in *Anesthesiology* and *Anesthesia and Analgesia*. Area of the state represents the percentage share of scientific papers published in both journals during 1990 or 1965 (inset). A state's total number of articles is presented next to each state abbreviation, if the number of articles was three or more. Below the state total is the number of articles from institutions with five or more articles. UW, University of Washington; MC, Mayo Clinic; MCW, Medical College of Wisconsin; UCSF, University of California, San Francisco; Stan, Stanford University; UCSD, University of California, San Diego; UI, University of Iowa; UIL, University of Illinois; U Pit, University of Pittsburgh; U Pen, University of Pennsylvania; TJU, Thomas Jefferson University; UTH, University of Texas at Houston; UAB, University of Alabama at Birmingham; WFU, Wake Forest University; JH, Johns Hopkins University.

does not reflect publications in journals other than *Anesthesiology* and *Anesthesia and Analgesia* and therefore is far from being complete. However, we strongly believe that the most important anesthesiology-related investigations are usually published in these two journals, and the map is indicative of the contributions to research in anesthesiology.

Igor Kissin, MD, PhD
Pamela T. Brown, BS
Melinda L. Johannson, BA
Department of Anesthesiology
University of Alabama at Birmingham
Birmingham, AL 35294

Comments by the Editor-in-Chief

The above letter by Kissin et al. was accepted for publication because it represented an interesting analysis regarding the source of a major component of anesthesia literature. However, the readers should recognize that the analysis of Kissin et al. places prime importance on numbers of articles rather than quality. At the recent annual meeting of the International Anesthesia Research Society, Dr. Nicholas Greene, the former Editor-in-Chief of *Anesthesia and Analgesia* cautioned that the rapid increase in the number of uninteresting or irrelevant publications makes it more difficult to identify the important contributions to our literature. It is unfortunate that Kissin et al. did not emphasize relevance and importance rather than numbers of publications.

Ronald D. Miller, MD

Alternative Chin-Support Device During Face Mask Anesthesia

To the Editor:

Syringes and tongue depressors are simple and effective chin-supporting devices; however, they may compress nerves and vessels against the inferior border of the mandible and, if displaced, press against the hyoid bone.

An alternative technique is to position the head on a ring and elevate the chin using a wide elasticized rubber strap, such as is used to exsanguinate a limb, centered over the point of the chin so that a centimeter of the strap covers the lower edge of the rubber mask. Each length of the strap is carefully tensioned and led back along the mandible and border of the ear to be secured to the table in the midline (see Figure 1). As with other devices, inspection and adjustment are necessary if the patient is moved on the table. This is a convenient and atraumatic way to improve airway maintenance and is particularly useful in bearded patients.

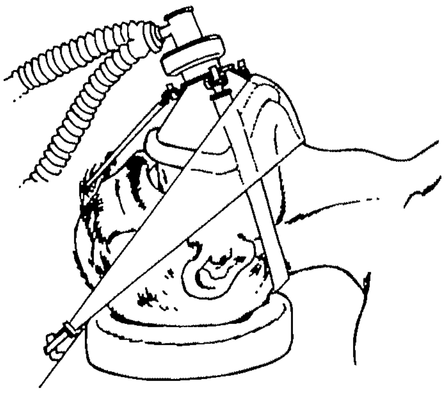

Figure 1. A rubber strap chin support.

R. John Elton, MB, ChB, FCAnaes
Department of Anesthesiology
The University of Texas Health Science Center at Houston
6431 Fannin, 5.020 MSMB
Houston, TX 77030

Reference

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Bleeding Diathesis After Perioperative Ketorolac

To the Editor:

Ketorolac, recently added to the postoperative pain arsenal, is promoted as an efficacious analgesic without the adverse side effects of narcotics (1). At our institution we recently had a perioperative complication that might be attributed in part to ketorolac. Given the newness of this drug and the paucity of literature regarding its complications, this report may heighten awareness of complications attributable to ketorolac and perhaps better define or limit the use of this agent.

A 65-yr-old man recently had total knee reconstruction under spinal anesthesia using bupivacaine and morphine. Preoperative history was remarkable for hypertension and degenerative joint disease, for which he had been taking hydrochlorothiazide and atenolol. Although the orthopedic service often gives coumadin preoperatively to patients having total joint replacement, in this instance coumadin was not administered preoperatively because a regional anesthetic was planned. Postoperatively, the patient was given ketorolac for analgesia, starting with a 60-mg IM loading dose, followed by 30-mg IM doses every 6 h for 24 h. Simultaneously, the orthopedic service prescribed 10 mg of oral coumadin daily. Five days postoperatively the patient experienced gastric bleeding, with a decrease in hematocrit from 33% to 19% and with elevated prothrombin and partial thromboplastin times at 20 and 43 s (normal values of 10.8–13.0 and 21.0–32.0 s, respectively). This bleeding required 18 U of packed red blood cells, 14 U of fresh frozen plasma, and admission to the intensive care unit for a day of monitoring. Thereafter his postoperative course was uneventful, and he left the hospital on the eighth postoperative day.

Upon further questioning, the patient disclosed that before surgery he had been taking 10–14 aspirin tablets daily but denied any previous ulcer history. Whether the patient's postoperative gastrointestinal bleeding was caused by platelet dysfunction secondary to the use of aspirin, to coumadin, to ketorolac, to a combination of the foregoing, or to preexisting gastric pathology remained unclear. As a nonsteroidal drug, ketorolac can cause gastrointestinal distress. Perhaps ketorolac should be avoided in patients who may be predisposed to bleeding diatheses by their history or medications.

Barbara M. Fleming, MD
Dennis W. Coombs, MD
Dartmouth-Hitchcock Medical Center
2 Maynard Street
Hanover, NH 03756

Reference

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A Hidden Leak in the Circle System

To the Editor:

As new anesthesia equipment becomes a part of clinical practice, new causes of leaks will be discovered. We describe a case in which we detected a "hidden" leak associated with the Ohmeda 5500 Airway Pressure Monitor, which is designed to indicate changes in the circle system pressure (Figure 1) and to alarm if a set pressure limit is exceeded (1). Besides the problem of leak, such a disconnection generates a falsely low reading of airway pressure that is potentially hazardous.

We were performing a routine preoperative check of our anesthesia machine (Ohmeda Modulus II). To check for leaks, we closed the adjustable pressure-limiting valve, occluded the Y-piece, and pressurized the circuit to 30 cm H_2O. We noticed a steady decline of the value on the absorber pressure gauge. We were unsuccessful in detecting the source and elected to use a different machine. Later the original machine was rechecked. We found that the Ohmeda 5500 Pressure Monitor did not show any indication of change in pressure with change in the circuit pressure, i.e., the green PAW activity LED bar graph did not illuminate up and down as it should. When the monitor was taken out of its housing, the pressure tubing connecting the back of the monitor to the circuit was found to be disconnected (Figure 2). When reconnected the leak disappeared. We also noticed that the pressure reading of the absorber pressure gauge increased markedly at that point, but dropped down as soon as the pressure tubing was disconnected again to confirm our findings.

The Ohmeda Airway Pressure Monitor is an added potential source of leak if the tubing connecting it to the circuit is disconnected or torn, and this could be overlooked, especially as much of the tubing is hidden from view. The tubing goes from the circuit at the absorber pressure gauge to the side of the anesthesia machine in open view, but the remainder of it is hidden within the anesthesia machine.

Another important observation is the decrease in the reading of the absorber pressure gauge if there is a disconnection (Figure 2). In this instance, the absorber pressure gauge will not reflect the true pressure in the circuit, owing to the fact that the airway pressure monitor tubing is connected to the circuit via the same common connection as the absorber pressure gauge (Figure 1).

We attempted to quantify the magnitude of the leak caused by this disconnection. With the breathing bag removed and this opening as well as the Y-piece occluded, 650 mL/min of fresh gas flow was required to maintain the pressure gauge reading stable at 30 cm H_2O with the tubing disconnected. The decrease in the pressure reading was assessed by reattaching the breathing bag, keeping the Y-piece occluded, and pressurizing the circuit to 43 cm H_2O (Figure 1). The tubing was then disconnected from the back of the monitor, and the absorber pressure gauge reading instantaneously decreased 10–12 cm H_2O. As the leak continued and the distended breathing bag continued to empty, the pressure reading continued to decline (Figure 2).

This disconnection was called to the manufacturer's attention through the service representative. A different type of tubing that should be less prone to disconnection has been added to our machine. However, the potential for tubing disconnection always exists. The manufacturer's "preoperative checkout procedure" recommends not using the airway pressure monitor if it fails any checkout test (1). This procedure states the bar graph should be checked for motion as the circuit is pressurized, but it fails to mention any cause for failure of graph motion and recommends no course of action other than not using the monitor. However, not using the monitor will not fix the leak problem and, in fact, may mask it even further. We believe the manufacturer should mention this potential and easily correctable source of leak in their recommended "preoperative checkout procedure."

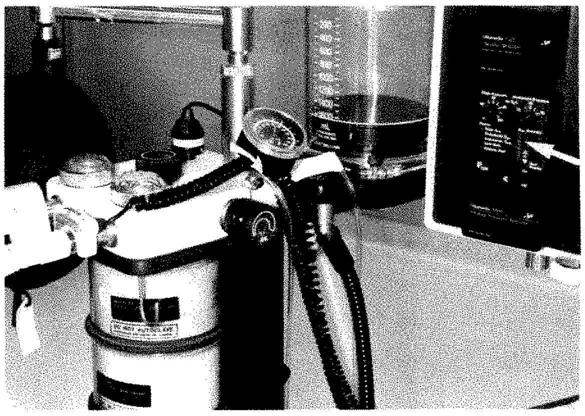

Figure 1. The Ohmeda 5500 Airway Pressure Monitor on the far right showing the lighted bars (*straight arrow*) indicating an increase in the circuit pressure. Connection of the pressure tubing with the circuit is shown at the *curved arrow*.

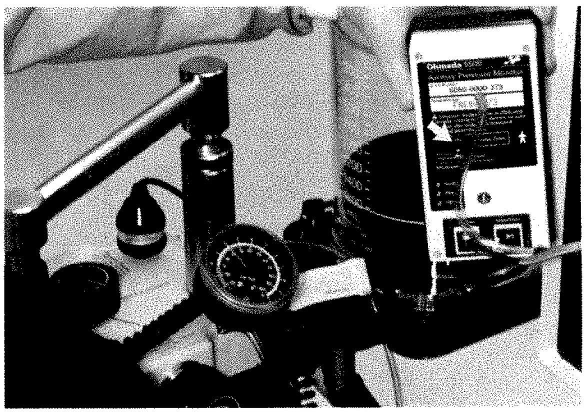

Figure 2. The back of the Ohmeda 5500 Airway Pressure Monitor after taking it out of its housing with the pressure tubing disconnected (site of disconnection indicated by *arrow*).

Kamal Yassin, MD
James J. Gibbons, MD
Department of Anesthesiology
St. Louis University
St. Louis, MO 63110

Reference

1. Ohmeda 5500 Airway Pressure Monitor operations and maintenance manual. The BOC Group, 1987.

Endrate or Amidate

To the Editor:

Etomidate injection (Amidate, Abbott Laboratories, North Chicago, Ill.) in our hospital is supplied in 20-mL glass ampules. There is a similarly packaged drug that could cause serious problems if it were administered in place of etomidate. Edetate disodium (Endrate, Abbott Laboratories) is a seldom-used chelating agent, which produces a rapid decrease in serum calcium concentration when administered intravenously. Hypocalcemic tetany, seizures, and severe cardiac arrhythmias can ensue. Edetate has a negative inotropic effect on the heart and transiently antagonizes the inotropic and chronotropic effects of digitalis. Therefore, it is clinically useful in the treatment of refractory ventricular arrhythmias associated with digitalis toxicity. Emergency treatment of hypercalcemia is another possible use for this drug. Whenever it is administered, it must be diluted and then given by slow infusion to minimize adverse reactions (1).

There are a number of ways in which Amidate and Endrate could be confused. Their trade names are somewhat similar, both being short words ending in "ate." Both drugs are supplied in 20-mL ampules, which at first appear identical, and come packaged five to a box (Figure 1). In the instance that I am citing, one ampule of Endrate had been unintentionally placed in a box of Amidate ampules. It was only after retrieving the incorrect ampule from the pharmacy and returning to the operating room that the careful observer noted the error. In this case a catastrophe was avoided, but one step in the sequence of a drug administration error had already occurred: that is, the pharmacy did not detect the imposter before dispensing it to us.

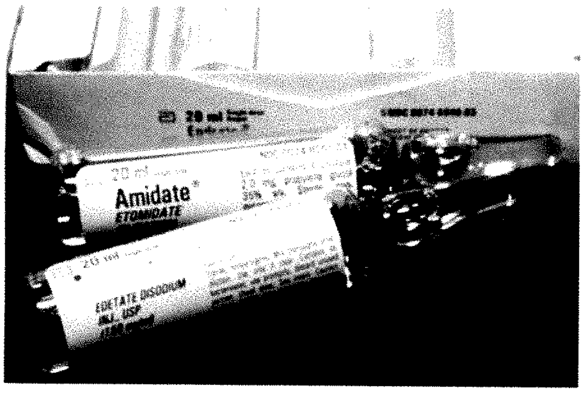

Figure 1. Amidate and Endrate, two very different drugs, are found in identical-sized vials, which may increase the possibility of their being accidentally substituted for each other.

Every day we are confronted by potential traps. This is just one more instance that emphasizes that careful attention to detail is paramount in our daily practice. In fairness to the manufacturer, there is a warning in red on the label which states "Caution: Must Be Diluted." Nonetheless, the similarities are remarkable and provide an environment in which error is more likely to occur. Abbott Laboratories has been notified.

James L. Murphy, Jr., MD
Department of Anesthesiology
The Ohio State University Hospital
Columbus, OH 43210

Reference

1. McEvoy GE, ed. American hospital formulary service drug information supplement A. Hyattsville, Md: Taylor Printing, 1989:1657.

Lack of Interaction Between Prior Succinylcholine Administration and Doxacurium-Induced Neuromuscular Block

To the Editor:

I would like to point out an error concerning doxacurium in the recent article by Dubois et al. (1) on the effects of prior succinylcholine administration on the neuromuscular blocking effects of pancuronium and pipecuronium. In their discussion, they indicate that under certain circumstances potentiation of doxacurium-induced block has been observed after prior succinylcholine administration. Both the statement and the literature citation (2), which refer to work on atracurium rather than doxacurium, are incorrect. The interaction of succinylcholine and doxacurium has been investigated by three groups [Forbes et al. (3), Katz et al. (4), and Lynam et al. (5)], all of which concluded that there was no clinically significant interaction between succinylcholine and doxacurium.

Martha M. Abou-Donia, PhD
Department of Clinical Neuroscience
Burroughs Wellcome Co.
Research Triangle Park, NC 27709

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1. Dubois MY, Fleming NW, Lea DE. Effects of succinylcholine on the pharmacodynamics of pipecuronium and pancuronium. Anesth Analg 1991;72:364-8.
2. Stirt JA, Katz RL, Murray AL, Schehland DL, Lee C. Modification of atracurium blockade by halothane and by suxamethonium. Br J Anaesth 1983;55:S71-5.
3. Forbes RB, Mehta MP, Murray DJ, et al. Effect of succinylcholine on subsequent neuromuscular blockade with BW A938U. Anesthesiology 1987;67:A363.
4. Katz JA, Fragen RJ, Shanks CA, Dunn K, McNulty B, Rudd D. The effects of succinylcholine on doxacurium-induced neuromuscular blockade. Anesthesiology 1988;69:604-7.
5. Lynam DP, Caldwell JE, Miller RD. Onset time, maximum blockade, spontaneous recovery and clinical duration of action of doxacurium chloride during narcotic anesthesia with and without prior administration of succinylcholine. Anesthesiology 1988;69:A884.

In Response:

We appreciate the interest of Dr. Abou-Donia in our recent study of pipecuronium and its interactions with succinylcholine (1). She is correct in pointing out a misstatement, missed in our editorial process. Stirt et al. (2) demonstrated changes in the response to atracurium (not doxacurium) after full recovery from succinylcholine-induced neuromuscular blockade. However, studies of interactions between doxacurium and succinylcholine have also produced conflicting conclusions. Forbes et al. (3) studied 18 patients under N_2O/narcotic/barbiturate anesthesia, comparing the response to doxacurium with or without prior treatment with succinylcholine. They demonstrated a 26% decrease in the time to maximum blockade and a 42% increase in the recovery time. Both effects were statistically significant. In contrast, studies by Lynam et al. (4) and Katz et al. (5) failed to demonstrate any significant interactions.

We believe the interesting question raised by these studies is not just whether a particular drug produces a response that may be judged to be clinically significant, but rather, what characteristics of a neuromuscular blocking drug or of a study protocol combine to produce the observed responses. These issues are clearly and completely discussed by Katz et al. (5).

Michel Y. Dubois, MD
Neal W. Fleming, MD, PhD
Dawn E. Lea, RN, BSN
Department of Anesthesia
Georgetown University Medical Center
3800 Reservoir Road NW
Washington, DC 20007

References

1. Dubois MY, Fleming NW, Lea DE. Effects of succinylcholine on the pharmacodynamics of pipecuronium and pancuronium. Anesth Analg 1991;72:364–8.
2. Stirt JA, Katz RL, Murray AL, Schehland DL, Lee C. Modification of atracurium blockade by halothane and by suxamethonium. Br J Anaesth 1983;55:S71–5.
3. Forbes RB, Mehta MP, Murray DJ, et al. Effect of succinylcholine on subsequent neuromuscular blockade with BW A938U. Anesthesiology 1987;67:A363.
4. Lynam DP, Caldwell JE, Miller RD. Onset time, maximum blockade, spontaneous recovery and clinical duration of action of doxacurium chloride during narcotic anesthesia with and without prior administration of succinylcholine. Anesthesiology 1988;69:A884.
5. Katz JA, Fragen RJ, Shanks CA, Dunn K, McNulty B, Rudd D. The effects of succinylcholine on doxacurium-induced neuromuscular blockade. Anesthesiology 1988; 69:604–7.

Additional Factor Related to Suction Trauma

To the Editor:

In their interesting clinical report, Bogetz et al. (1) have suggested that pharyngeal suctioning with excessively negative pressure predisposes to pharyngeal trauma. Our experience with the following patient supports this relationship and additionally suggests that the type of suction catheter used may be equally important.

The patient was a healthy 38-yr-old woman who was scheduled for removal of a mandibular bone plate. After an atraumatic nasal preparation was performed with lidocaine and phenylephrine, general anesthesia was induced and a 7.0 nasal endotracheal tube was passed into the pharynx. On laryngoscopy, we noted some clear secretions with a small amount of blood in the posterior pharynx. Therefore, the pharynx was cleared using a Yankauer-tipped catheter. As laryngoscopy continued and as the endotracheal tube was manipulated by the use of Magill forceps, an increasing amount of blood was noted, which required one additional use of suction. After appropriate placement of the endotracheal tube, we noted a 5-mm, round, punctate lesion on the right tonsillar pillar that was oozing a small amount of blood. Although we considered a number of other possibilities, the resemblance of the lesion to the size of the suction hole on the Yankauer-tipped catheter suggested a relationship between the two.

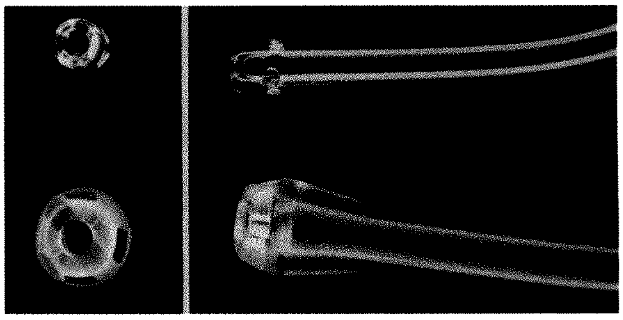

Figure 1. Views of two Yankauer catheters demonstrating the marked differences in design.

To investigate this relationship, we first measured the suction pressure and found it to be 500 mm Hg; a pressure much greater than the recommendation by Dorsch and Dorsch (2) of approximately 180 mm Hg. However, because this suction pressure was not a new phenomenon for our operating rooms and because pharyngeal trauma had not been previously reported, we suspected that the introduction of a new Yankauer-tipped catheter to our operating room may have played a role. Therefore, the ease of soft tissue aspiration into the catheter was determined for the new narrow-tipped Yankauer catheter with small side holes and for our previously used larger blunt-tipped Yankauer catheter with larger side holes (Fig. 1). Our investigations led us to believe that the design of the catheter can markedly influence the ability of the catheter to aspirate soft tissue at a given negative pressure. We suggest that the use of the larger blunt-tipped catheter is less likely to produce pharyngeal trauma from the aspiration of soft tissue into the catheter.

Daniel M. Podeschi, MD
David H. Sprague, MD
Department of Anesthesiology
University of North Carolina Hospitals
Chapel Hill, NC 27599-7010

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1. Bogetz MS, Tupper BJ, Vigil AC. Too much of a good thing: uvula trauma caused by overzealous suctioning. Anesth Analg 1991;72:125–6.
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A "New" Brachial Plexus Block: Some Questions and Objections

To the Editor:

It is important, as Moorthy et al. (1) pointed out, that the degree of risk and the success rate of a new technique for supraclavicular plexus block be considered. Their approach was interesting and their complication rate low. However, I am not sure that the initial results indicate a higher success rate than that found with other techniques. In their series of 82 cases using a lateral paravascular block, 61 patients (72%) had good surgical anesthesia, 12 required supplementation, and 9 required general anesthesia. In a larger series of cases (300), Balas (2), using the perivascular approach described by Winnie and Collins (3), reported a 95.33% success rate. Significant complications in the form of pneumothorax did occur, however, in 2.67% of cases. Moorthy et al. state that the failure rate associated with the lateral paravascular technique decreased with increasing experience, and therefore, the results of this technique, after it has been established, will be of interest to all anesthesiologists who wish to maintain patient satisfaction with minimal risk.

Timothy W. Rutter, MD
Department of Anesthesiology
University of Michigan Medical Center
1500 East Medical Center Drive UH-1G323
Ann Arbor, MI 48109-0048

References

1. Moorthy SS, Schmidt SI, Dierdorf SF, Rosenfeld SH, Anagnostou JM. A supraclavicular lateral paravascular approach for brachial plexus regional anesthesia. Anesth Analg 1991;72:241–4.
2. Balas GI. Regional anesthesia for surgery on the shoulder. Anesth Analg 1971;50:1036–41.
3. Winnie AP, Collins VJ. The subclavian perivascular technique of brachial plexus anesthesia. Anesthesiology 1964;25:353–63.

To the Editor:

The recent article by Moorthy et al. (1) raises several points:

1. Why was the failure rate so high (either a block works or it doesn't) (28%) despite a "Doppler," a nerve stimulator, and a large volume (50 mL) of anesthetic? In good hands, Winnie's interscalene or subclavian blocks achieve a near 100% success rate without special locators and with smaller volumes (35–40 mL) (2). Were the failures caused by misplacement of the anesthetic outside the perivascular sheath or to incomplete bathing of the cervicobrachial plexus by a too distal spread of the solution within the sheath? Radiographic studies or cadaver dissections may have answered the question.
2. Using a nerve stimulator for a brachial plexus block does not guarantee correct needle placement as a needle outside of the sheath may stimulate the motor fibers through the fascia (2,3).
3. The authors' claim that their approach prevents pneumothoraxes is unconvincing; any supraclavicular needle directed downward and outward may inadvertently puncture the pleura.
4. Why did the authors choose the term "para" (para = near, beside) over "perivascular" (implying needle placement in the perivascular sheath)? Their text and Dr. Gibbs' drawing suggest that they indeed sought needle entry into that sheath. Why did they not retain then the accepted "perivascular" adjective?
5. It is unclear whether the block was used for arteriovenous access in patients with renal failure. One would think that such debilitated heparinized patients are poor candidates for an experimental technique with a potential for pneumothorax and dangerous subclavian hematoma. An axillary route (preferably not transarterial) would seem to be a wiser alternative.

Ray J. Defalque, MD
Department of Anesthesiology
University of Alabama
Birmingham, AL 35233

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1. Moorthy SS, Schmidt SI, Dierdorf SF, Rosenfeld SH, Anagnostou JM. A supraclavicular lateral paravascular approach for brachial plexus regional anesthesia. Anesth Analg 1991;72:241–4.
2. Winnie AP. Plexus anesthesia. Volume I. Philadelphia: WB Saunders 1990:215.
3. Goldberg ME, Gregg C, Larijani GE, et al. A comparison of three methods of axillary approach to brachial plexus blockade for upper extremity surgery. Anesthesiology 1987;66:814–6.

In Response:

We thank Dr. T. W. Rutter and Dr. R. J. Defalque for their comments on our recent article (1). The failure rate reported in the article was dependent on two important factors: (a) the development of a new method associated with the process of learning, and (b) a teaching institution where the residents perform the procedure under supervision. Though the randomized study is not yet ready, the success rate for the new block when performed by the authors is nearly 100%. As Dr. Defalque has suggested, further studies will help determine the cause of block failures when they occur. The use of a nerve stimulator as we described it is well tolerated by the patients and gives a high percentage of success. One of the causes of block failure is needle movement while injecting the drug.

The possibility of pneumothorax is minimized by our technique because the needle is lateral to the third part of the subclavian artery and to the first part of the axillary artery and because the brachial plexus is lateral to the artery (2,3). This anatomic relationship illustrates that the point of needle insertion and the direction of the needle advancement clearly avoid the apex of the pleura, a statement that cannot be made for the traditional perivascular block.

The technique has been developed after our extensive research on anatomy and dissection in cadavers. The artery and the brachial plexus in the axilla, posterior to pectoralis minor, are in fat, loose areolar tissue and fascia. In addition, this method does not puncture the artery and does not elicit paresthesias associated with pain, hematoma, and associated complications. We believe that the new brachial plexus block is more dense and longer lasting than the conventional axillary plexus block.

S. S. Moorthy, MD
Jonathan M. Anagnostou, MD
Stephen F. Dierdorf, MD
Department of Anesthesia
Indiana University School of Medicine
Indianapolis, Indiana

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1. Moorthy SS, Schmidt SI, Dierdorf SF, Rosenfeld SH, Anagnostou JM. A supraclavicular lateral paravascular approach for brachial plexus regional anesthesia. Anesth Analg 1991;72:241–4.
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Section Editor
Norig Ellison

Book Reviews

Recalled to Life. The Story of a Coma

Esther Goshen-Göttstein. New Haven: Yale University Press, 1990, 208 pp, $25.00.

This is an unusual book to be reviewed in a scientific journal but contained within its pages is a great deal of information relevant not only to American anesthesiologists but also to those concerned with intensive care throughout the world. The medicoscientific facts of the case are reported in the *Postgraduate Medical Journal* (Volume 66, pages 381–6, 1990).

This is a story of the author's 60-yr-old husband and his journey from a vegetative state to one of almost total recovery: as a professor of linguistics, his skills in writing, teaching, and lecturing have returned to their former high calibre 4 yr later. The roles of his family and friends are painstakingly recorded together with all the frustrations that accompanied his recovery. Recent legal decisions in the United States do not lessen the impact of this careful and authentic account, and I strongly recommend that everyone should spend the necessary 2 to 3 hours to read this little book.

J. N. Lunn
University of Wales College of Medicine
Heath Park, Cardiff, United Kingdom

Manual of Complications During Anesthesia

Nikolaus Gravenstein, ed. Philadephia: J. B. Lippincott Company, 1991, 722 pp.

Complications During Anesthesia is a deceptive little book. On initial examination, one wonders how a 722-page paperback volume can possibly cover the subject of complications during anesthesia in any detail. However, on closer examination the book does in fact do this. Dr. Gravenstein has managed to make this volume both complete and concise.

Although multiauthored, each of the authors is from the University of Florida, or other Florida institutions, with the exception of one author from the University of Colorado. This perhaps helps explain the cohesiveness of the volume.

A few typos exist; the most notable one found appears in the table on the management of anaphylaxis and recommends as initial therapy: 1. stop the administration of oxygen! In addition, some sections are not as well referenced as I would like. For example, isoflurane is said to be associated with more nausea and vomiting than either halothane or enflurane. Although I do not disbelieve this, it is not a widely held opinion, and as such, needs a reference. Most subjects in this manual are well organized, to the point, and infinitely practical. There are many well-chosen illustrations, and in general, the many tables make it very useful as a quick reference manual.

In short, I would recommend this book to every resident studying for his board examinations as a "must read" and to every practicing anesthesiologist as a useful reference manual for his or her office library.

Susan W. Krechel, MD
University of Missouri-Columbia
Columbia, Missouri

Advances in Anesthesia. Volume 8

R. K. Stoelting, P. G. Barash, and T. J. Gallagher, eds. St. Louis: Mosby Year Book, 1991, 341 pp., $59.95.

The editors are to be commended for again selecting a group of authors, some familiar to most readers and others newer to the specialty, who have produced a series of well-edited and well-referenced chapters of interest to the practicing anesthesiologist. The topics are diverse and inevitably the reader will choose those of personal interest first, at least this reviewer did. The chapter on the alternatives to perioperative blood transfusion by members of the Department of Laboratory Medicine at Yale is comprehensive and contains many up-to-date references. There is, however, one conspicuous flaw. The description of the technique and apparatus for harvesting platelet-rich plasma indicates that shed plasma is salvaged for reinfusion. There is a semiautomated device that can be used in the operating room immediately before initiation of surgery for collection of platelet-rich plasma. However, there is no apparatus that selectively salvages shed plasma. The chapter on anesthetic evaluation for the reconstructed heart is not intended solely for the pediatric anesthesiologist. Patients who have had repairs of complex congenital cardiac defects present for a variety of operative procedures. The author points out that such patients often have improved hemodynamic status, but only infrequently have normal cardiovascular anatomy and physiology, necessitating individual evaluation and anesthetic management. The chapter on echocardiography in the operating room is readable and easily understood by those not conversant with the principles and applications of this technique. The group from San Antonio present a thorough review of the pathophysiology of spinal cord injury as well as guidelines for anesthetic management of the patients. Subscribers to *Anesthesiology* will find a remarkable similarity between the chapter on the role of α_2-agonists in anesthesia and the review in the March 1991 issue of the journal, including tables and figures. The more recent review contain 316 references, whereas the former has only 241. In the introductory paragraph of the chapter on the implications of nitrous oxide administration, Dr.

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Skaredoff indicates that he will provide data and recommendations to enable the reader to make an informed decision whether or not to include nitrous oxide in a given anesthetic plan. He accomplishes this goal in an unbiased manner. Any anesthesiologist contemplating organizing an acute pain management service would do well to read the chapter by Lubenow and Ivankovich. The protocols, policies, and procedures included in the appendix should prove particularly useful. Lack of reference to other chapters does not imply inferior quality. There are no dogs in this kennel.

Linda Stehling, MD
Albuquerque, New Mexico

Gas Man, Understanding Uptake and Distribution in Anesthesia and Analgesia, 2nd ed.

J. H. Philip. Chestnut Hill, Mass.: Med Man Simulations, 1991, 180 pp (software workbook), $245.00 (single); $645.00 (site license).

To the neophyte student of anesthesiology, the uptake and distribution of anesthetic gases is virtually incomprehensible. The pharmacokinetics and related physics are wholly dynamic and the phenomena requires a "hands-on" approach to fully grasp. The 1990 American Board of Anesthesiology In-Training Exam had seven subject areas addressing uptake and distribution. American medical school graduates in the clinical base year incorrectly answered these questions 68% of the time, and 47% of the time those finishing residency also answered incorrectly. The intertwining of numerous concepts necessary for successful appreciation of uptake, distribution, and elimination remains beyond the reach of many trainees. Gas Man is a teaching tool developed specifically to address this issue. The first version, which was introduced in 1982, has been updated and released for use on MACINTOSH computers. (An IBM-PC version is being developed.) Gas Man is based on pharmacokinetic principles introduced by S. Kety in the early 1950s and on data extensively developed by E.I. Eger II validating the model.

The success of Gas Man does not rely on flashy program techniques. Rather, it is the thorough and complete workbook accompanying the software program that makes it a valuable adjuvant for those teaching uptake and distribution. Gas Man approaches this subject via a logical series of laboratory exercises. The areas emphasized include alveolar gas tensions, blood:gas and blood:tissue partition concepts, venous return, and anesthesia machine:patient interactions. Low-flow anesthesia and closed circuits are covered and exercises are used to apply newly acquired knowledge to the administration of anesthetics. Typography and graphics are amply used to achieve several goals including ease of use, clear layout of lesson plans, and highlighting of the fundamentals to be learned. Examples of computer simulation outputs are used copiously to emphasize new ideas.

It is the computer-simulation portion of each exercise that brings uptake and distribution to "life." The standard MACINTOSH point and click technique permits quick mastery of the skills needed to manage each experiment. Every experiment has a "set-up" that is clear to follow; experienced users can quickly reference the setup panel, thus bypassing explanations aimed at the novice. The full series of experiments may take as long as 3 hours to conduct and the workbook correlates closely with the simulations, thereby providing a smooth and progressive road to understanding numerous concepts.

Gas Man cannot be all things to all people. As with all difficult concepts, Gas Man will not instantly teach uptake and distribution by virtue of its reliance on computer simulation. A dose of motivation is required to complete all the exercises. Nor is Gas Man a full-function simulator with refined physiologic models, multiple parameter envelopes, gas mass distribution tables, and graphic options enabling detailed investigation of every subtlety of uptake and distribution, or of anesthesia machines and patient pathophysiology. Finally, this package is costly, although it can be justifiably added to departmental libraries as a valuable addition to other educational materials.

With proper guidance, Gas Man is a useful self-teaching tool for medical students or residents trying to surmount the hurdles to knowledge in this area. Most important, the well-referenced workbook accompanying the Gas Man simulator provides a strong foundation upon which educators can build their approach to the teaching of uptake and distribution.

Dan Lawson, MD
University of Virginia Health Sciences Center
Charlottesville, Virginia

Principles of Transfusion Medicine

E. C. Rossi, T. L. Simon, and G. S. Moss, eds. Baltimore: Williams & Wilkins, 1991, 791 pp, $95.00.

During a 4-month period this reviewer used *Principles of Transfusion Medicine* as his primary reference in matters pertaining to the administration of blood and blood products to patients and was not once disappointed. On this side of the Atlantic, the book will undoubtedly replace Mollison's *Blood Transfusion in Clinical Medicine* as the standard to which other books on this subject are compared. In 16 sections covering topics from the red cell to organization of blood services are covered comprehensively and currently. The references at the end of each chapter are a nice mix of classic and current references, which will permit those interested in researching a subject in greater depth to do so, but sufficient information is provided that the reader is unlikely to find that necessary in making clinical decisions.

The sections on transfusion in the surgical patient and hemostasis and surgery will be of most interest to anesthesiologists. Indeed, these sections could stand alone as a monograph to be used in anesthesia residency programs. Interestingly, the editors conclude their preface by stating that, "Transfusion will remain in transition . . . this volume will help the readers anticipate those changes." The degree of changes is perhaps best illustrated by the conclusion of the chapter on preoperative hemodilution, "A hematocrit of 30% is adequate to prevent tissue or deficits in surgical patient." Today that figure seems unduly conservative to this reviewer with target values of 22%–24% being used commonly in otherwise healthy surgical patients.

Who should buy this book? All anesthesiologists would benefit by owning and frequently consulting it. Certainly all clinical departments should have a copy in their library. At $95.00 this reviewer rates *Principles of Transfusion Medicine* as a Best Buy!

Norig Ellison, MD
University of Pennsylvania
Philadelphia, Pennsylvania

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Aloia RC, Curtain CC, Gordon LM, eds. *Drug and Anesthetic Effects on Membrane Structure and Function,* Volume 5 of Advances in Membrane Fluidity. New York: John Wiley & Sons, 1991, 292 pp, $165.00.

Camporesi EM, Moon RE, eds. *Applications of Hyperbaric Oxygen.* Volume 4, No. 2 of Problems in Respiratory Care. Philadelphia: J.B. Lippincott, 1991, 136 pp, $27.00 single issue or $60.00 subscription for four issues.

Eichorn JH, ed. *Improving Anesthesia Outcome.* Volume 5, No. 2 of Problems in Anesthesia series. Philadelphia: J.B. Lippincott, 1991, 180 pp, $30.00 single issue or $70.00 subscription for four issues.

Litwack K, ed. *Pain and Post Anesthesia Management.* Volume 3, No. 1 of Critical Care Nursing Clinics of North America. Philadelphia: W.B. Saunders, 1991, 164 pp, $49.00 for subscription for four issues or $22.00 for single issue.

Max MB, Portenoy RK, Laska EM, eds. *The Design of Analgesic Clinical Trials.* Volume 18 of Advances in Pain Research and Therapy. New York: Raven Press, 1991, 751 pp, $122.00.

Murphy KR, Pelton JJ. *ECG Essentials, A Pocket Reference for Systematic Interpretation.* Chicago: Quintessence Books, 1991, 176 pp, $24.00.

Parbrook GD, David PD, Parbrook EO. *Basic Physics and Measurement in Anaesthesia,* 3rd ed. Boston: Butterworth Heinemann, 1990, 344 pp, $49.95.

Roberts JT, ed. *Fiberoptics in Anesthesia.* Volume 9, No. 1 of Anesthesiology Clinics of North America. Philadelphia: W.B. Saunders, 1991, 198 pp, $74.00 subscription for four issues or $30.00 for single issue.

Warfield CA. *Manual of Pain Management.* Philadelphia: J.B. Lippincott, 1991, 384 pp, $49.50

Needles: A Sticky Situation for U.S. Healthcare.

Healthcare workers in Americ are facing an epidemic problem - needle sticks. Each year thousand of healthcare workers ar accidentally stuck in hospitals, nursing hom nics and i general practice. se needle stick can lead to very ous infections, with at least 20 ent pathogen having been ide as transmitted in this way.

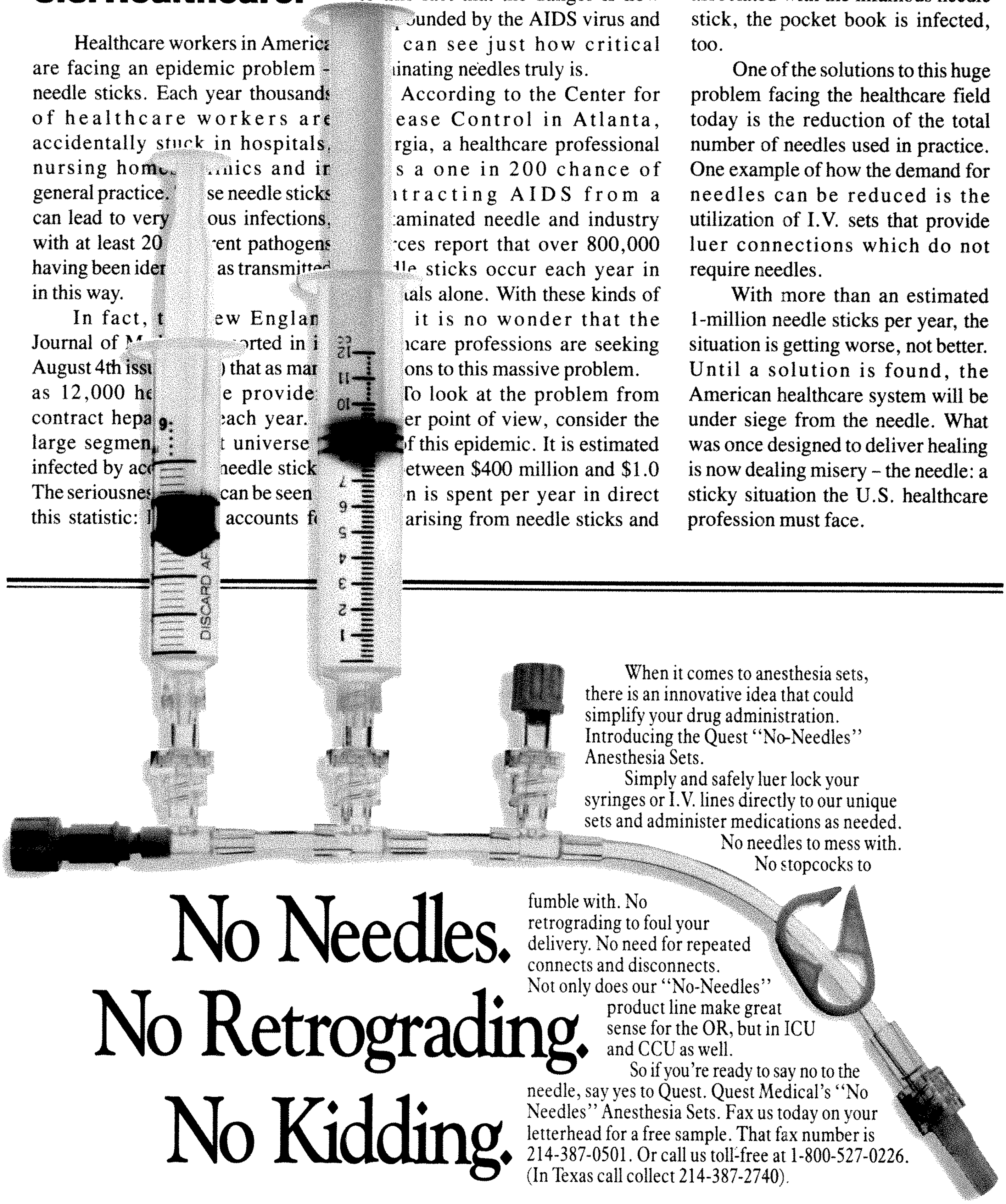
In fact, t ew Englan Journal of M rted in i August 4th iss) that as ma as 12,000 h e provide contract hepa each year. large segmen t universe infected by ac needle stick The seriousne can be seen this statistic: accounts f 200 to 300 deaths a year to healthcare providers. And the number is growing every year. Add to this fact that the danger is now unded by the AIDS virus and can see just how critical inating needles truly is.

According to the Center for ease Control in Atlanta, rgia, a healthcare professional s a one in 200 chance of tracting AIDS from a aminated needle and industry ces report that over 800,000 le sticks occur each year in als alone. With these kinds of it is no wonder that the care professions are seeking ons to this massive problem.

To look at the problem from er point of view, consider the f this epidemic. It is estimated etween $400 million and $1.0 n is spent per year in direct arising from needle sticks and this range does not include treatment or loss of work. In other words, aside from the human suffering associated with the infamous needle stick, the pocket book is infected, too.

One of the solutions to this huge problem facing the healthcare field today is the reduction of the total number of needles used in practice. One example of how the demand for needles can be reduced is the utilization of I.V. sets that provide luer connections which do not require needles.

With more than an estimated 1-million needle sticks per year, the situation is getting worse, not better. Until a solution is found, the American healthcare system will be under siege from the needle. What was once designed to deliver healing is now dealing misery - the needle: a sticky situation the U.S. healthcare profession must face.



When it comes to anesthesia sets, there is an innovative idea that could simplify your drug administration. Introducing the Quest "No-Needles" Anesthesia Sets.

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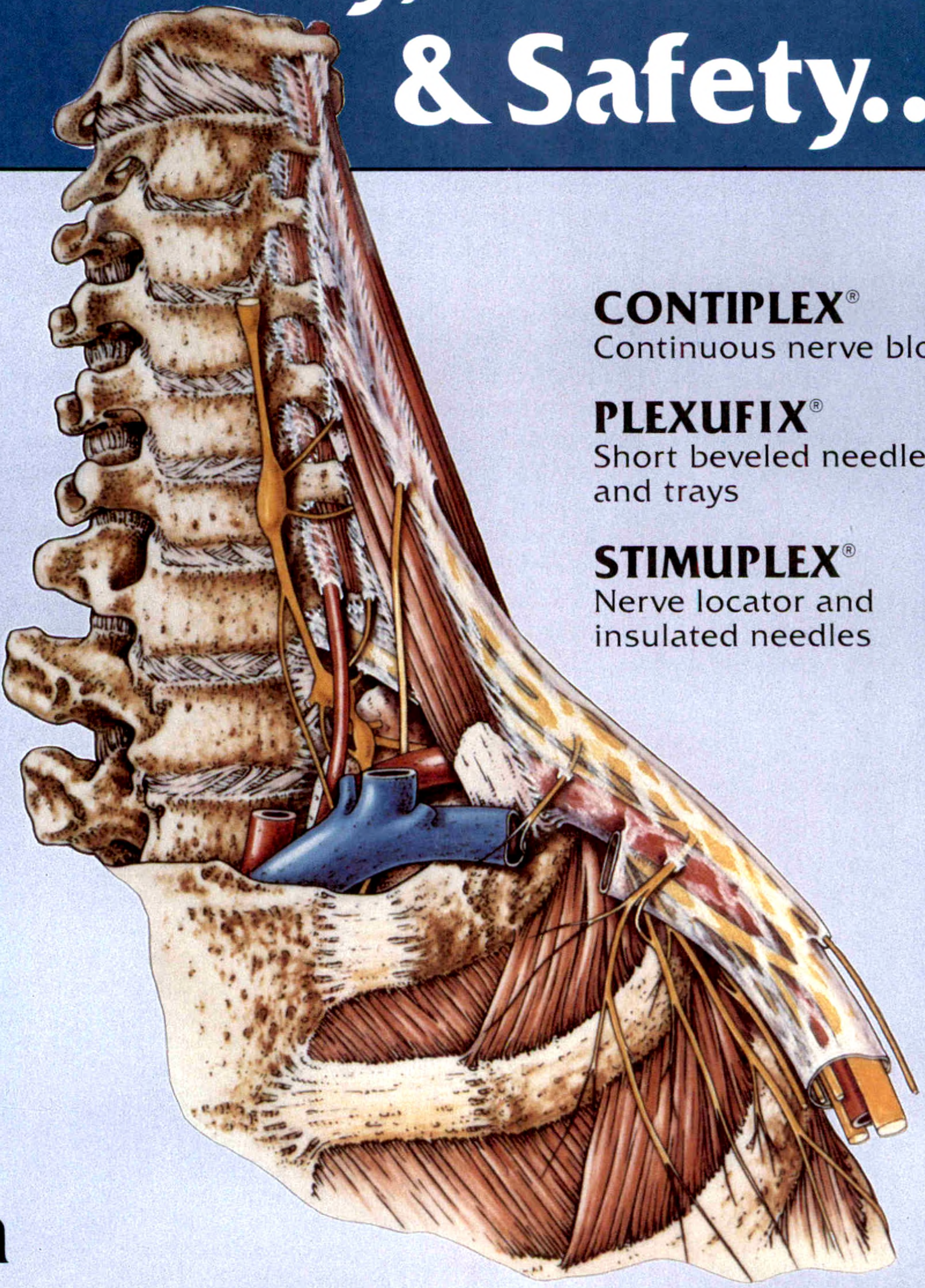

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The Netherlands JOURNAL OF MEDICINE

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PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

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Aims and Scope:

The Netherlands Journal of Medicine publishes original articles and reviews in all relevant fields of internal medicine. In addition to clinically oriented papers, manuscripts containing experimental data, including both laboratory and animal studies, are considered for publication. The "Bri Reports" section allows for the publication of concise reports on original work, while Case Reports, which are relevant for understanding the pathophysiology or clinical presentation of internal diseases may also be accepted under this heading. Furthermore, book reviews and a correspondence section are regular items in the Journal.

An International Advisory Board has been established, consisting of outstanding scientists, all distinguished investigators in various fields of intern medicine.

Since 1987 the Journal has been published in two editions: a monthly edition for the Netherlands audience and a bimonthly edition for the international audience.

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Cited/abstracted in: Current Contents (Clinical Medicine); Index Medicus (MEDLINE); Excerpta Medica (EMBASE); BIOSIS Database

Subscription information (Intl.Ed.):

1991: Vols. 38-39 (2 vols. in 12 issues)
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Long Island Jewish Medical Center is seeking several academic Anesthesiologists to join our expanding full time department. The Medical Center, a rapidly growing 825-bed tertiary care teaching center, conveniently located to both New York City and Long Island, provides a full range of patient care services including all the surgical specialties and obstetrics/gynecology.

Chief of Pediatric Anesthesiology
...who will direct pediatric anesthesiology practice at Schneider Children's Hospital, a division of the Long Island Jewish Medical Center, in which approximately 3,000 surgical procedures, including cardiothoracic, are performed yearly.

Chief of Cardiothoracic Anesthesiology
...who will direct a group of cardiothoracic anesthesiologists in an expanding adult surgical service within the Chasanoff Heart Institute at the Medical Center.

Chief of Obstetrical Anesthesiology
...who will direct and organize a new service of obstetrical anesthesiologists in a renovated labor and delivery facility, which cares for approximately 4,000 deliveries, including high-risk obstetrics, yearly.

Prerequisites include Board Certification with advanced subspecialty training and demonstrated performance in the clinical, teaching, and research components of that subspecialty practice.

Academic appointment at the Albert Einstein College of Medicine commensurate with qualifications. Compensation package is comprehensive and attractive.

Please submit a current CV and Bibliography in confidence to: Philip Lebowitz, MD, Chairman, Department of Anesthesiology, LIJMC, New Hyde Park, NY 11042.
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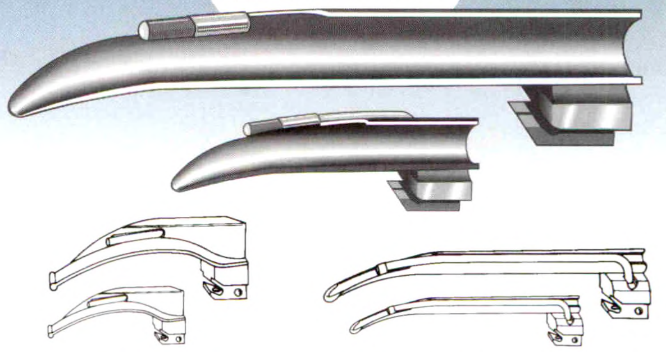

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CHAIRPERSON: DEPARTMENT OF PEDIATRIC ANESTHESIA. CHILDREN'S MEMORIAL HOSPITAL, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILLINOIS

Nationally recognized, 256 bed free-standing pediatric hospital seeks board certified anesthesiologist with academic leadership and administrative skills to run a department staffed with 14 board certified pediatric anesthesiologists and 4 CRNA's. Approximately 10,500 cases a year including all facets of pediatric anesthesia plus a 2 operating room surgicenter in one of the Western Suburbs. The candidate will be responsible for maintaining a successful teaching program, and developing a research program in basic sciences in a soon to be available new research building. The candidate should have extensive clinical experience in pediatric anesthesia, a proven record of scholarly activity and a commitment to graduate medical education. The candidate will hold an appropriate academic rank at Northwestern University Medical School. The candidate will assume the presidency of an already existing professional corporation which is responsible and is part of The Children's Memorial Faculty Practice Plan, Inc. Starting date will be January 1, 1992.

Applications accompanied by a detailed curriculum vitae and names of two individuals well known in academic circles for references should be directed to:

Frank Gonzalez-Crussi, M.D.
Chairman of Search Committee
Department of Pathology
Children's Memorial Hospital
2300 Children's Plaza
Chicago, IL 60614

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Department of Anesthesiology

The Department of Anesthesiology at the Dartmouth-Hitchcock Medical Center in Hanover, New Hampshire is seeking Board Certified/Board Eligible anesthesiologist to join the faculty.

The successful applicant should have formal training beyond the three-year continuum in subspecialty of anesthesiology practice or have recognized skills in a subspecialty area of anesthesiology in lieu of formal fellowship training. Pain management, pediatric anesthesiology and pediatric critical care would be particularly desirable. The successful candidate must have a commitment to teaching of medical students and residents, in addition to his/her own clinical expertise. The ability and desire to do clinical and/or basic research is essential.

The individual will be an employee of the Hitchcock Clinic and will receive an appropriate academic appointment as a member of the faculty of Dartmouth Medical School.

The Dartmouth-Hitchcock Medical Center is committed to Affirmative Action and is especially interested in identifying qualified female or minority candidates.

Inquiries and resumes should be directed to the Chair of the Search Committee: D. David Glass, M.D., Professor and Chair, Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, 2 Maynard Street, Hanover, NH 03756.

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The Department of Cardiothoracic Anesthesia, Cleveland Clinic Foundation is seeking applications from those interested in 6 months or one-year CA 3/4 subspecialty training. The experience encompasses the perioperative management of over 4000 patients scheduled for all major cardiac and thoracic procedures. Such positions are available in July, 1991 or January, 1992. Opportunities for clinical research accompany the vast clinical training.

Interested candidates should write to:

Dr. Erik J. Kraenzler
Department of Cardiothoracic Anesthesia
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9500 Euclid Avenue
Cleveland, Ohio 44195

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Albany Medical College has immediate openings for BC/BE Anesthesiologists to join our staff of 25 MDs, over 30 CRNAs and 30 residents to provide team-approach anesthesia care for all types of cases. Interest in research and teaching is highly desirable.

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

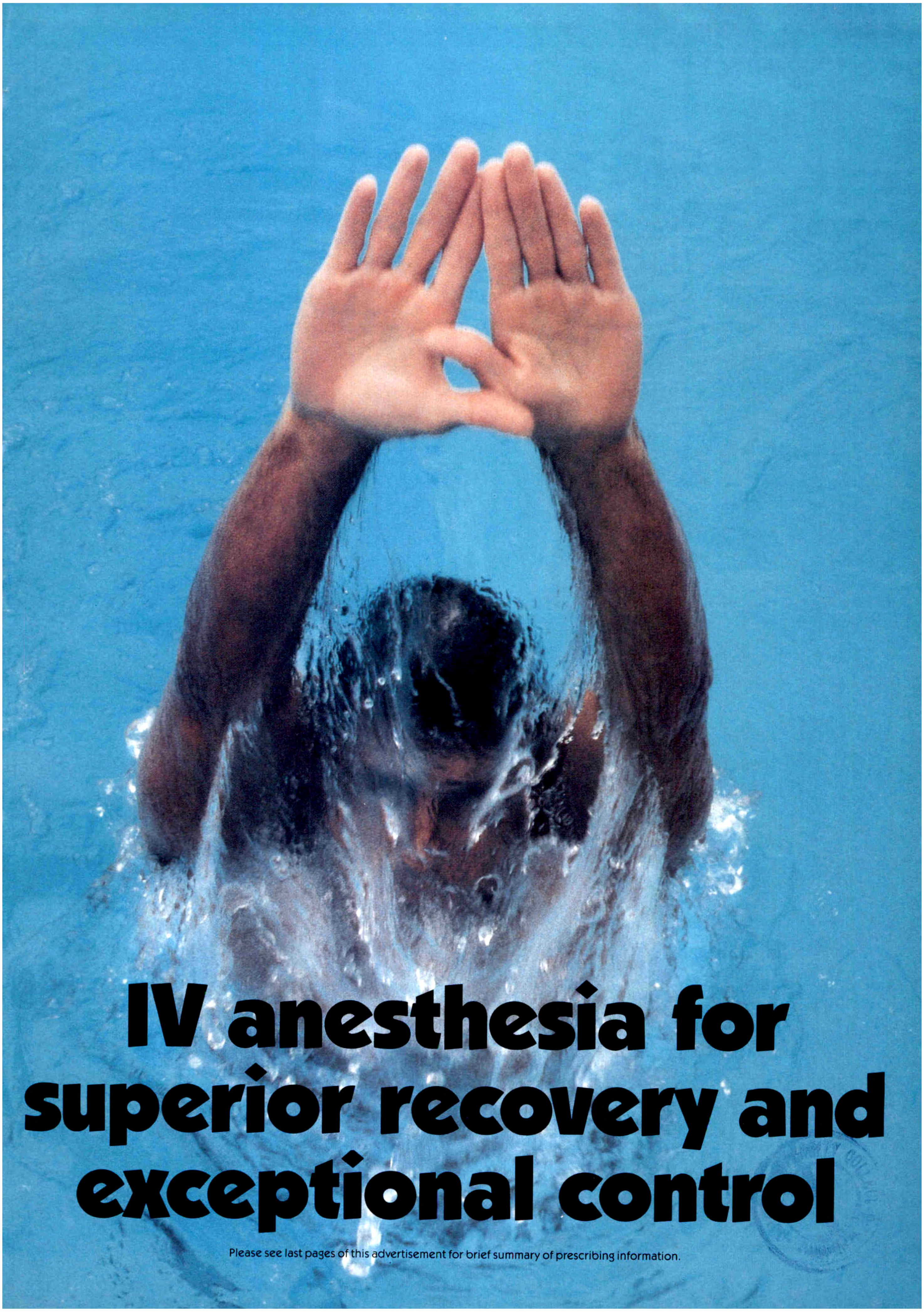
1992 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1992 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than December 13, 1991. Where relevant, applications must include institutional approval of human studies and/or animal research.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
2 Summit Park Dr., #140
Cleveland, OH 44131
Telephone: (216) 642-1124

The 1992 Award(s) will be announced at the Annual Scientific Meeting (66th Congress) of the International Anesthesia Research Society to be held at the San Francisco Hilton on Hilton Square, March 13–17, 1992.



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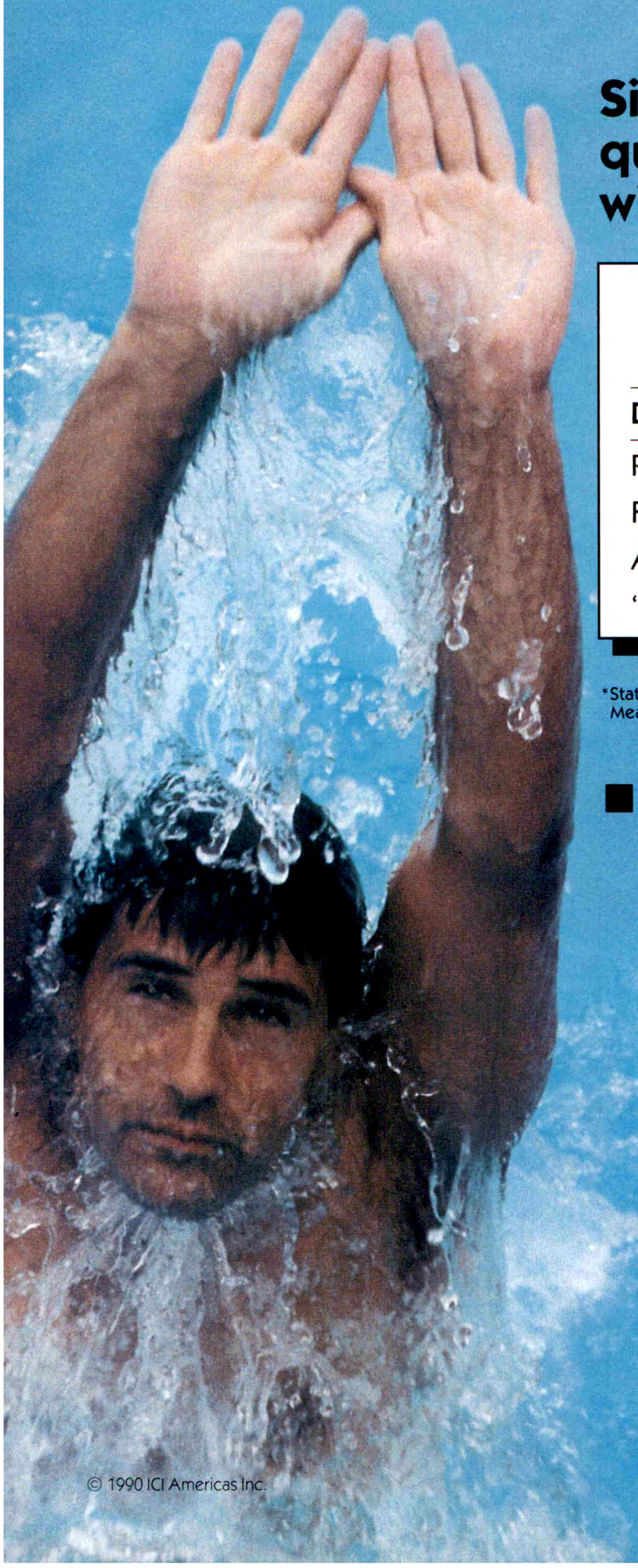
exceptional



Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

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recover and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

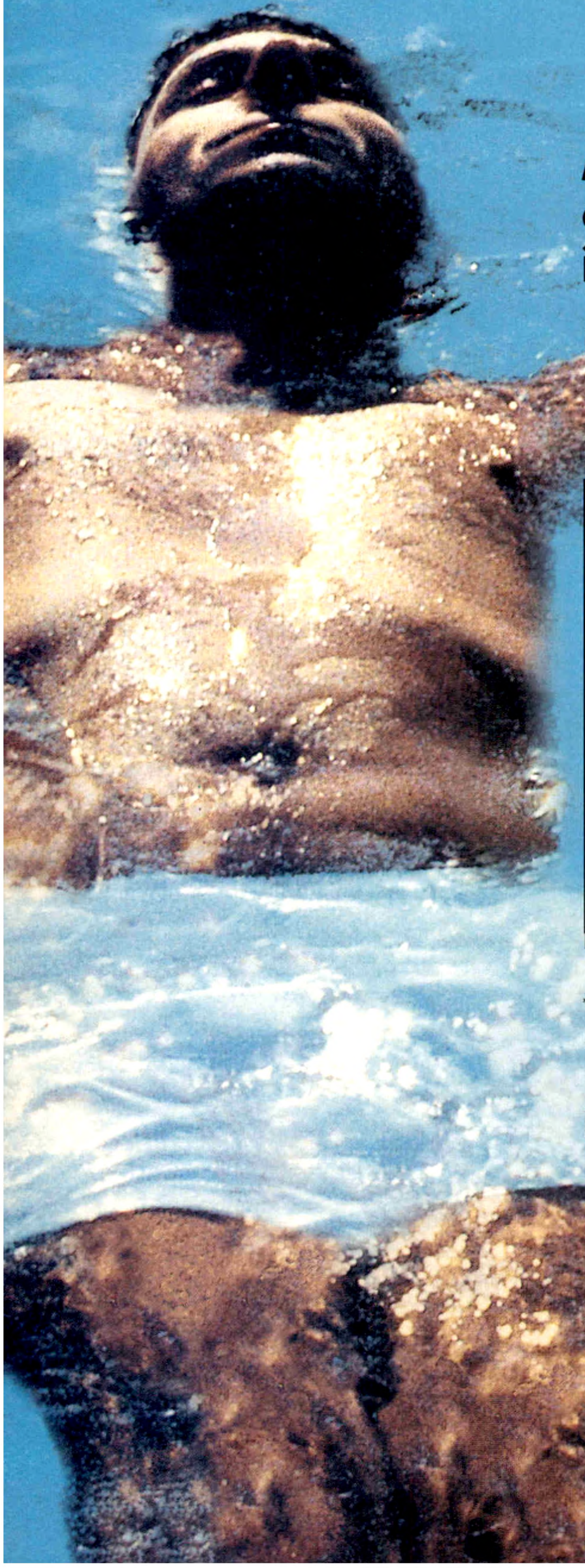
Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®

INJECTION

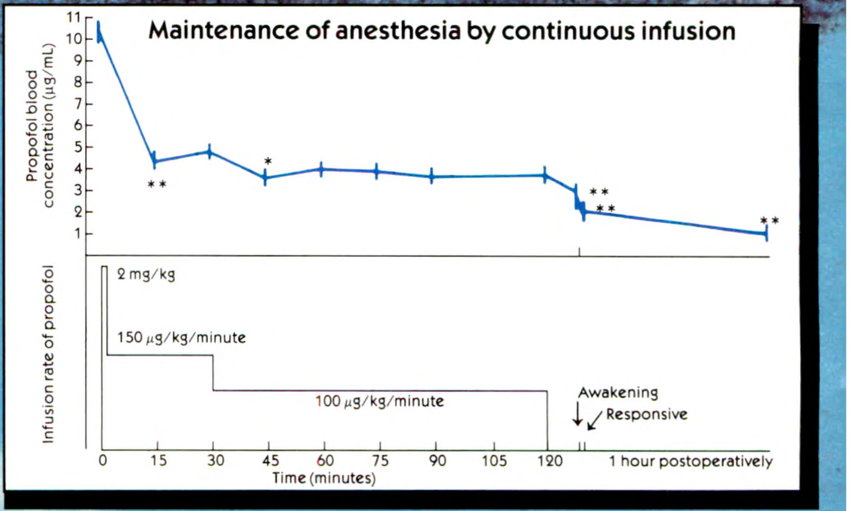
propofol



Superior exceptional

Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.

**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recover[illegible], and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.
[†] Induction dose requirements may be reduced.

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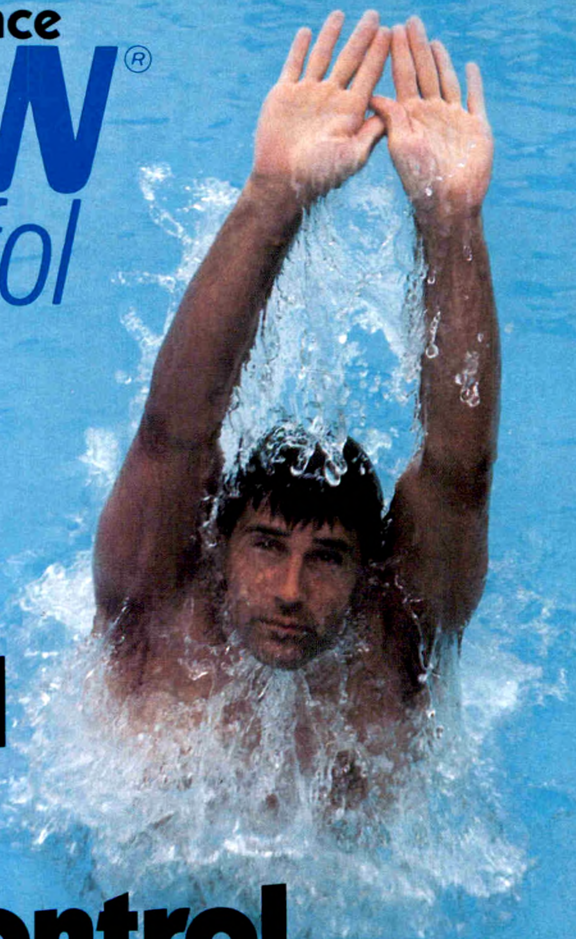
For induction and maintenance

DIPRIVAN®
INJECTION
propofol



For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: **1.** Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. **2.** Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. **3.** Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. **4.** Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. **5.** Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

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DIPRIVAN®

INJECTION
10 mg/mL
propofol

EMULSION FOR IV ADMINISTRATION
(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.) **CONTRAINDICATIONS:** When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components. **WARNINGS:** DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.** DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known. **Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.) PRECAUTIONS: General:** A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home. When DIPRIVAN Injection is administered to an epileptic patient, there may be a risk of convulsion during the recovery phase. Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae. Perioperative myoclonia, rarely including convulsions and opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear. DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli. **Information for Patients:** Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia. **Drug Interactions:** The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. **Nursing Mothers:** DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. **Pediatric Use:** DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. **Neurosurgical Anesthesia:** Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures. **ADVERSE REACTIONS:** Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. **Incidence Greater than 1%—All events regardless of causality, derived from clinical trials. Body as a Whole:** Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement*, Headache, Dizziness, Twitching, Bucking/Jerking/ Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea**, Vomiting*, Abdominal Cramping. **Injection Site:** Burning/Stinging**, Pain**, Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing. Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater. **Incidence Less than 1%—Causal Relationship Probable** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*) **Body as a Whole:** Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/

Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine*. **Incidence Less than 1%—Causal Relationship Unknown** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*) **Cardiovascular:** Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, *Myocardial Ischemia*. **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus*. **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia*. **Special Senses:** Ear Pain, *Nystagmus*. **Urogenital:** Abnormal Urine. **DRUG ABUSE AND DEPENDENCE:** None known. **OVERDOSAGE:** To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents. The intravenous LD_{50} values are 53 mg/kg in mice and 42 mg/kg in rats. **DOSAGE AND ADMINISTRATION: Induction:** Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.) Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction. **Maintenance:** Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections. When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates. **Continuous Infusion:** DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times. **Intermittent Bolus:** Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic, and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion**—titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration. **Dilution Prior to Administration:** When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.) **Administration Into a Running IV Catheter:** Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter: 5% Dextrose Injection, USP; Lactated Ringers Injection, USP; Lactated Ringers and 5% Dextrose Injection; 5% Dextrose and 0.45% Sodium Chloride Injection, USP; 5% Dextrose and 0.2% Sodium Chloride Injection, USP. **Handling Procedures:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. DIPRIVAN Injection must not be administered through a microbiological filter because this could restrict the flow of DIPRIVAN and/or cause the breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion. Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When using vials with volumetric infusion devices insert sterile vent spike through rubber stopper and immediately connect IV line. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection, reservoirs, IV lines or solutions containing DIPRIVAN Injection must be discarded at the end of the anesthetic procedure. Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness. *Aseptic Technique* for Handling DIPRIVAN Injection Ampules:* • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask and hair cover. • Disinfect neck surface of ampule using 70% isopropyl alcohol. Swab neck of ampule by wiping in one direction and let dry. • Protect fingers and hands by using sterile gauze when opening the ampule. • Withdraw DIPRIVAN Injection into a sterile syringe. • Immediately replace needle cap and discard ampule. • Label syringe with appropriate information, including date, time and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours—whichever occurs sooner. *Aseptic Technique* for Handling DIPRIVAN Injection Vials (and for Use With Volumetric Infusion Devices):* • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask and hair cover. • Remove metal cap from vial. • Disinfect rubber stopper of vial using 70% isopropyl alcohol. Wipe in one direction and let dry. • Insert sterile vent spike through rubber stopper and remove luer cap. • Connect a sterile syringe(s) to vent spike and withdraw entire contents; (Or when using volumetric infusion devices, aseptically connect IV line to vent spike). • Immediately cap syringe(s) with sterile closure(s) and discard vial and vent spike. • Label syringe(s) (or vial when using volumetric infusion devices) with appropriate information, including date, time and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours—whichever occurs sooner. *These techniques are not intended to preempt more stringent, established institutional guidelines for the aseptic handling and administration of sterile parenteral drug products. **HOW SUPPLIED:** DIPRIVAN Injection is available in ready to use 20 mL ampules and 50 mL infusion vials containing 10 mg/mL of propofol.
20 mL ampules (NDC 0038-0290-20) 50 mL infusion vials (NDC 0038-0290-50)
Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

Rev D 02/91

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How to talk about drug abuse in the presurgical interview

ASK your patients if they use illegal drugs. Explain the possible effects of interactions with OR medications, and the long-term health risks of drug abuse.

LOOK for signs of drug abuse: avoidance of eye contact, increased motor activity, compulsive behavior, extreme nervousness, or dilation of the pupils.

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Classified Advertising

FLORIDA
BC/BE anesthesiologist for expanding ambulatory group practice. Part time/full time with no nights, emergencies, OB, or weekends. Please reply to Box 621C/L.

621C/L

ILLINOIS
Anesthesiologist to join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approx. 40,000 (35 mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 624C/H.

624C/H

FULL-TIME ANESTHESIOLOGIST
BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to Lake Charles Anesthesiology, 1415 18th Street, Lake Charles, LA 70601.

634C/H

ANESTHESIOLOGY CA-4 CRITICAL CARE MEDICINE
CA-4 training in Critical Care Medicine satisfying the requirement for certification of specialty competence in critical care medicine through anesthesiology. Newly approved program at the Albany Medical Center. Two positions available for July 1991. Send CV to Carol Kiner, Albany Medical Center, Anesthesia A-131, Albany, NY 12208.

631D/I

ADIRONDACK—LAKE CHAMPLAIN REGION
Upstate New York—growing, active department seeks additional BC/BE anesthesiologist. Limited OB, neuro, and pediatrics; no open heart. Excellent starting salary. Close to Montreal and the Olympic-Lake Placid region. If you enjoy skiing and sailing, contact us for more details: Hannah Hanford, P.O. Box 1656, Plattsburgh, NY 12901; (518) 643-2998.

665E/H

POSTDOCTORAL FELLOWSHIP
Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

674E/D

Immediate positions available for part-time anesthesiologists, Monday through Friday, 7:00 AM to 3:30 PM (no call), to join a group of 17 anesthesiologists and 11 CRNAs in northwestern Indiana, 35 min from downtown Chicago. Excellent compensation package. Contact (219) 922-6366 or send curriculum vitae to Box 684F/I.

684F/I

Anesthesiologists needed at assistant, associate, and professor levels. Must be board certified or board eligible. Duties include patient care, resident and medical student teaching, and research. Positions available at the University of Missouri-Columbia Health Sciences Center. Interested applicants send curriculum vitae to G.W.N. Eggers, Jr, MD, Professor and Chairman, Department of Anesthesiology, University of Missouri Health Sciences Center, Columbia, MO 65212. An Equal Opportunity/Affirmative Action Employer.

691F/H

ANESTHESIOLOGIST
BC/BE to join small group practicing in a desirable city serving a metropolitan area of 500,000. All types of anesthesia including open heart. Fine school systems, residential areas, and recreational possibilities. Excellent benefits. Please send CV. Reply to Box 699G/I.

699G/I

PART-TIME
Anesthesiologist for south Georgia to join corporate group of MD and CRNAs. No open heart, no neurosurgery, no routine OB. One hour from Georgia and Florida beaches. Work only 26 weeks a year. Excellent opportunity to slow down. Full details first letter. Reply to Box 700G/I

700G/I

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

701G/L

DIRECTOR—DEPARTMENT OF ANESTHESIA
Florida—Miami Children's Hospital is seeking an experienced pediatric anesthesiologist as director. The hospital is a 206-bed, free-standing, tertiary-care facility located in a suburban area adjacent to Coral Gables. Interested applicants should submit a curriculum vitae and the names of

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CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum 1/4 page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

three references to Stanley B. Smith, MD, Miami Children's Hospital, Department of Pathology, 6125 S.W. 31 Street, Miami, FL 33155.

703GH

MISSOURI
Suburban K.C., need congenial partner for relaxed practice. No OB, neuro, cardiac. Maximum benefits; three-weeks on/off cycle leaves time for family, travel, locums. (816) 781-4580 evenings.

705GH

MASSACHUSETTS
Board-certified anesthesiologist sought to join group practice at a free-standing ambulatory surgical center in central Massachusetts. Full spectrum of day surgical cases. No nights or weekends. Seeking a committed, affable, flexible individual to share a pleasant, efficient, and modern working environment. Attractive salary and benefits leading to partnership opportunity. Please send CV to Box 712GH.

712GH

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF CALIFORNIA, DAVIS, MEDICAL CENTER
Two full-time faculty positions in the Salaried Clinical Professor series. Level of appointment will be commensurate with credentials. Responsibilities include (clinical educator) primarily clinical service with some teaching in the clinical setting. Applicants with training and/or experience in intensive care, OB, pediatrics, ambulatory and pain are preferred. Board certification or in-process of certification is required along with California licensure eligibility. Send curriculum vitae, bibliography, and names of three to five (3–5) references to John H. Eisele, Jr, MD, Professor and Chairman, Department of Anesthesiology, University of California, Davis, Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. Position open until August 31, 1991. We are an Equal Opportunity/Affirmative Action Employer.

713GH

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY
The Department of Anesthesiology at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in Cardiovascular Anesthesiology beginning July 1992. The fellowship is a 2-year, comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conferences, and teaching responsibilities are part of the fellowship experience. Interested individuals should contact Jorge Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico, 2211 Lomas Blvd. NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

730H/K

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology has an immediate opening for a Veterans Administration Chief of Service for Anesthesia at the New Mexico Regional Medical Facility (VA Hospital) in Albuquerque. Requirements include proven administrative, teaching, and leadership abilities, academic experience, and board certification. Appointment will be at the Associate Professor level. Qualified candidates should send CV or contact: Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

731H/K

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology has faculty positions beginning July 1992 for the following: (1) Obstetrical Anesthesia at the Assistant, Associate, or Full Professor levels; (2) Critical Care Medicine at the Assistant or Associate Professor level. It is expected that candidates for CCM positions will have or be eligible for subspecialty certification. Faculty responsibilities include provision of clinical care, teaching, and research. Qualified candidates should send CV or contact: Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

732H/K

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology has faculty positions at the Instructor, Assistant Professor, and Associate Professor levels beginning July 1992. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to: Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

733H/K

AVAILABLE IMMEDIATELY
in the Greater Cleveland Area a position for an MD anesthesiologist with Fellowship and or Pain Management. Department has a very rapidly growing Pain Management Center, wide variety of blocks and invasive procedures performed. Active ongoing research. Must be able to contribute significantly to the growth in this area, in addition to operating room duties. No OB or hearts. Excellent compensation and benefits leading to early partnership. If interested apply to Box 734HI with current CV.

734HI

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, PAIN MANAGEMENT
Faculty positions available for board certified/eligible anesthesiologists whose primary clinical responsibilities would be in a well-organized Pain Management Center run by the Department of Anesthesia. This position is available in the In Residence or Clinical series at the Assistant, Associate, or Professor level. Must have at least 5 years of postgraduate training, including research or other clinical training. Duties to also include patient care, resident and medical student teaching, and research or specialized clinical activity. California medical license required. Send correspondence, curriculum vitae, and list of professional referees to Ronald D. Miller, MD, Professor and Chairman, UCSF, Department of Anesthesia, Box 0648, Room C-455, 521 Parnassus Avenue, San Francisco, CA 94143-0648. The University of California is an Equal Opportunity Employer.

735HI

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
Faculty positions are available for board certified/eligible anesthesiologists. Must have at least 5 years of postgraduate training, including research or other intensive clinical training. Duties include patient care, resident and student teaching, research or specialized clinical activity, and administrative responsibilities. Special areas of interest may include any aspect of anesthesia. California medical license or eligibility for licensure is required. The University of California is an Equal Opportunity Affirmative Action Employer. Please forward curriculum vitae and three references to Ronald D. Miller, MD, Professor and Chairman, Department of Anesthesia, UCSF, 521 Parnassus Avenue, Box 0648, Room C-455, San Francisco, CA 94143-0648.

736HI

PENNSYLVANIA
Anesthesiologist—board certified/board eligible to join a fee-for-service group of five

anesthesiologists and seven CRNAs. Prerequisite of PGIV or equivalent. 250-Bed inner-city hospital located close to metropolitan area. Reply to Box 737H/J.

737H/J

PENNSYLVANIA
Immediate opening for BC/BE anesthesiologist to join 2 MDs and CRNAs in PA. Fee for service. Call Dr. Shah, (717) 242-7186, 9 PM to 5 PM.

623H

PAIN MANAGEMENT FELLOWSHIP
Unique training opportunity for highly motivated, patient-oriented, anesthesiologist to participate in strong clinical pain management program. Emphasis on comprehensive evaluation and the use of neural blockade in the treatment of acute, chronic, and cancer pain. Training in interventional pain management techniques including implantable drug delivery systems and CT-guided neurodestructive procedures.

Applicant must possess strong interest in regional anesthesia and desire one-on-one patient contact. No OR or OB anesthesia responsibilities. Applicant MUST be BC/BE in anesthesia before beginning training. Fellowship period—1 year. Interested applicants should send CV to Pain Consortium of Greater Kansas City, 11111 Nall #202, Leawood, KS 66221.

714H/A

Assistant Professor Clinical Anesthesiology for university medical center. Majority clinical duties in ophthalmology. Require Florida medical license and certification or eligibility for certification by American Board of Anesthesiology. Duties include teaching medical students and resident physicians in clinical anesthesia and supervising operation of biochemical pharmacology laboratory doing basic research on pharmacological agents used in anesthesia. Requires 3 years experience in biochemical research. Hours 8 AM to 5 PM Monday–Friday (40 hours/week + minimum 4 hours/week on call and further time as required). Salary $1,829/week. Apply by resume to Job Service of Florida, Mezzanine, 701 SW 27 Avenue, Miami, FL 33133, ref. J.O. #FL 0439945.

715H

VERMONT
Second anesthesiologist for growing department. Modern, 80-bed, acute care hospital. Fee-for-service practice. Lakeside community near excellent skiing. Income guarantee. Moving expenses. Send CV to New England Health Search, 63 Forest Avenue, Orono, ME 04473. Call (207) 866-5680.

716HI

PENNSYLVANIA
The Albert Einstein Medical Center has one faculty position available. Clinical responsibility is for all types of cases except cardiac. Interest in teaching residents required; interest in research preferred. Over 12,000 anesthetics performed annually. Modern 600-bed tertiary hospital. Major affiliate of Temple University. Interested applicants should reply with CV to Jonathan Roth, MD, Department of Anesthesiology, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141. (215) 456-7979.

717HI

PENNSYLVANIA
The Albert Einstein Medical Center has CA3 and CA4 positions available for 3- or 6-month rotations in Pain Management starting January or July 1992. Primarily clinical responsibilities, with research opportunities available for the interested individual. Interested applicants should reply with CV to Jonathan Roth, MD, Department of Anesthesiology, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141. (215) 456-7979.

718HI

PENNSYLVANIA
The Albert Einstein Medical Center has CA3 and CA4 positions available for 6- or 12-month rotations in adult Cardiac Anesthesia starting January or July 1992. Primarily clinical responsibilities, with research opportunities available for the interested individual. Interested applicants should reply with CV to Jonathan Roth, MD, Department of Anesthesiology, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141. (215) 456-7979.

719HI

PENNSYLVANIA
The Albert Einstein Medical Center is seeking a Director of Anesthesia Research. We are seeking a PhD, but will consider applications from qualified PharmD or MD candidates. Salary guarantee and seed funding available. Successful candidate will be expected to expand departmental program by nurturing and assisting junior faculty in addition to conducting individual investigation. Interested applicants should reply with CV to Jonathan Roth, MD, Department of Anesthesiology, Albert Einstein Medical Center, 5501 Old York Road, Philadelphia, PA 19141. (215) 456-7979.

720HI

WASHINGTON, D.C.
Positions available immediately and during the next year for full-time BE/BC anesthesiologists to join a growing MD/CRNA practice. Large ambulatory and challenging tertiary care caseload including all specialties except pediatrics at university-affiliated hospital. Reasonable call schedule with competitive compensation package and partnership after 1 year. Send or fax CV to Barney S.H. Feinstein, MD, Chairman, Department of Anesthesia, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010; Fax number (202) 877-5564 or call collect (202) 877-7500.

721H/A

FELLOWSHIP TRAINING, PEDIATRIC ANESTHESIOLOGY
Baylor College of Medicine, Department of Anesthesiology and its Pediatric Anesthesiology Division at Texas Children's Hospital offer 1- or 2-year subspecialty training in pediatric anesthesiology beginning January 1992. Texas Children's Hospital, a 300-bed facility, is a primary academic affiliate of Baylor College of Medicine. Ten new operating rooms open September 1991. Current case load, 7500 cases per year, spans the range of pediatric anesthesia. Opportunities are available during this training period to gain experience in neonatal critical care, critical care medicine, operating room, pain medicine, and ongoing clinical and laboratory research efforts. Requirements: satisfactory completion of an approved residency training program in anesthesiology in North America; currently in the American Board of Anesthesiology certification process; eligibility for unrestricted medical license, Texas. Salary: $29,000. Send current curriculum vitae and three references to Burdett S. Dunbar, MD, Chief, Pediatric Anesthesiology, Texas Children's Hospital, 6621 Fannin Street, Mail Code 4.158, Houston TX 77030.

722H

PEDIATRIC ANESTHESIOLOGIST: FACULTY POSITIONS
The Department of Anesthesiology, Baylor College of Medicine and its Pediatric Anesthesiology Division at Texas Children's Hospital are recruiting faculty at all academic levels. Ten new operating rooms open September 1991. 7500 cases per year span the range of pediatric anesthesia. The training program includes 10 trainees at the CA II level and beyond. This is an opportunity for pediatric anesthesia specialists who wish to combine clinical practice in a growing, academically oriented division with hospitable living in the economically resurgent climate of Houston, Texas. Successful applicants will be board certified in anesthesiology or will be in the board examination process and will be eligible for a Texas license. A minimum of 1-year pediatric anesthesia specialty training at the CA IV level or beyond is expected. Equivalents are these: current clinical practice, limited to pediatric anesthesia, or board certification in pediatrics. Research interests are desirable and will be encouraged through appropriate amounts of nonclinical time. Salary levels are competitive. Baylor is an equal opportunity employer. Send current curriculum vitae and three references to Burdett S. Dunbar, MD, Chief, Anesthesi-

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723H

Department of Anesthesiology, University of California, San Diego is recruiting for four positions at all ranks. One position is the Director of the UCSD Pain Management Program. Applicants for this position must have experience in all aspects of inpatient and outpatient pain management and have extensive experience in pain research and treatment. Applicants must demonstrate motivation to expand a pain management center and be able to direct a clinical pain research program involving protocol-driven human studies. The three other positions require experience in teaching and clinical training, patient care, and research interest or experience is preferred. One position requires demonstrated experience in critical care. One position requires subspecialty training and experience in obstetric anesthesia. One of the four positions may be tenured track. Otherwise the positions are non-tenured track. Rank and salary commensurate with experience and based on the UCSD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in anesthesiology and a California medical license is required. Possession of a certificate of special qualifications in Critical Care Medicine or eligibility to take the qualifying exam is required for the critical care position. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770-A, University of California San Diego Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California, San Diego is an Equal Opportunity/AA Employer. All applications received by October 31, 1991 will receive thorough consideration.

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CONTRAINDICATIONS: None known.
WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more suitable for these patients.
PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.
Renal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.
Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.
Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.
Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.
Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.
Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate anesthesia.
Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.
Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.
Drug/Laboratory Test Interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.
Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section.
Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a µg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED_{95}. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed, therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T_1 to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.
ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:
Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.
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When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.
CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES
1. Data on file.
2. Foldes FF, Nagashima H, Nguyen HD, Duncalf D, Goldiner PL. Neuromuscular and cardiovascular effects of pipecuronium. *Can J Anaesth*. 1990;37(5): 549-555.
3. Larijani GE, Bartkowski RR, Azad SS, et al. Clinical pharmacology of pipecuronium bromide. *Anesth Analg*. 1989;68:734-739.
4. Tassonyi E, Neidheart P, Pittet J-F, Morel DR, Gemperle M. Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology*. 1988;69(5):793-796.

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References: 1. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology. 1982; 56:112-118. 2. Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg. 1985;64:897-910. 3. Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology. 1986;65:A516. Abstract. 4. Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stresss associated with worse outcome? Anesthesiology. 1987;67:A1. Abstract. 5. Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology. 1987;66:130-135.

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PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society

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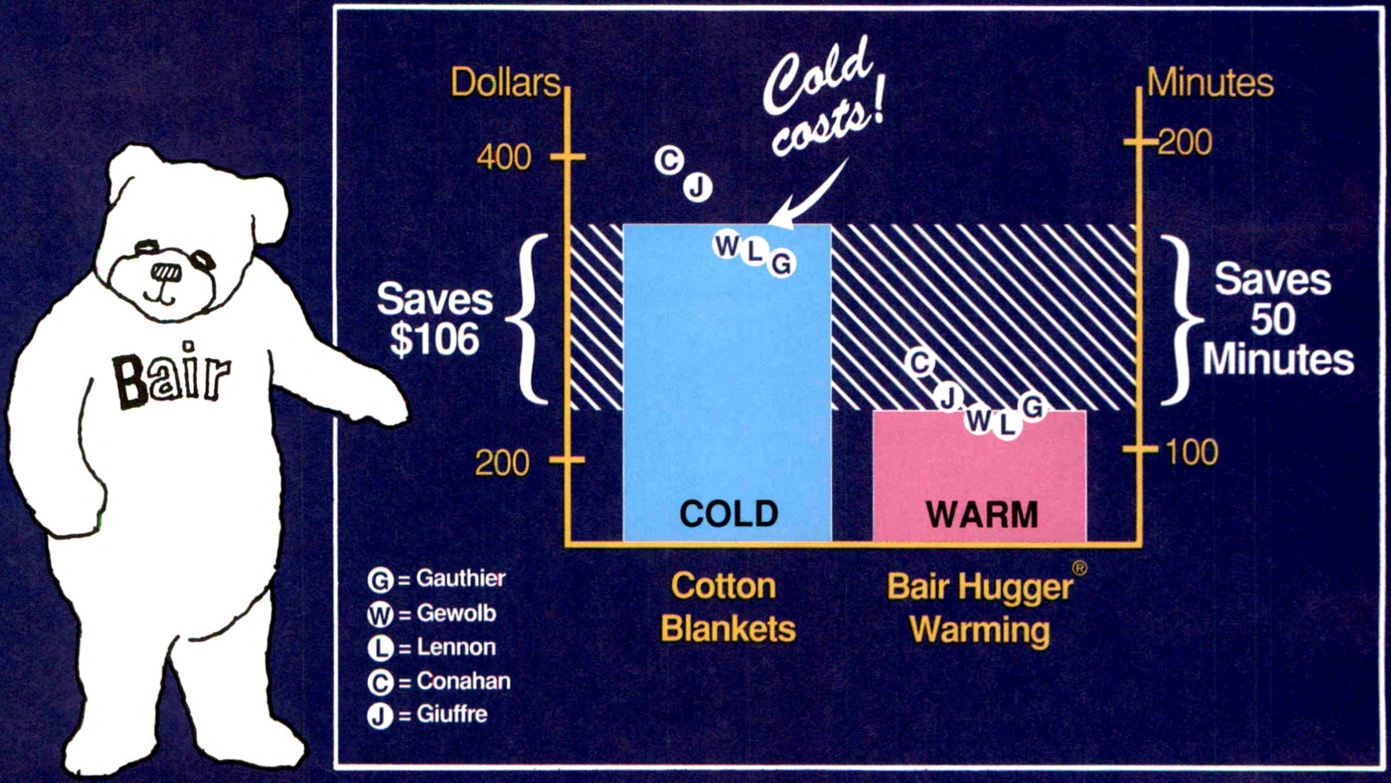

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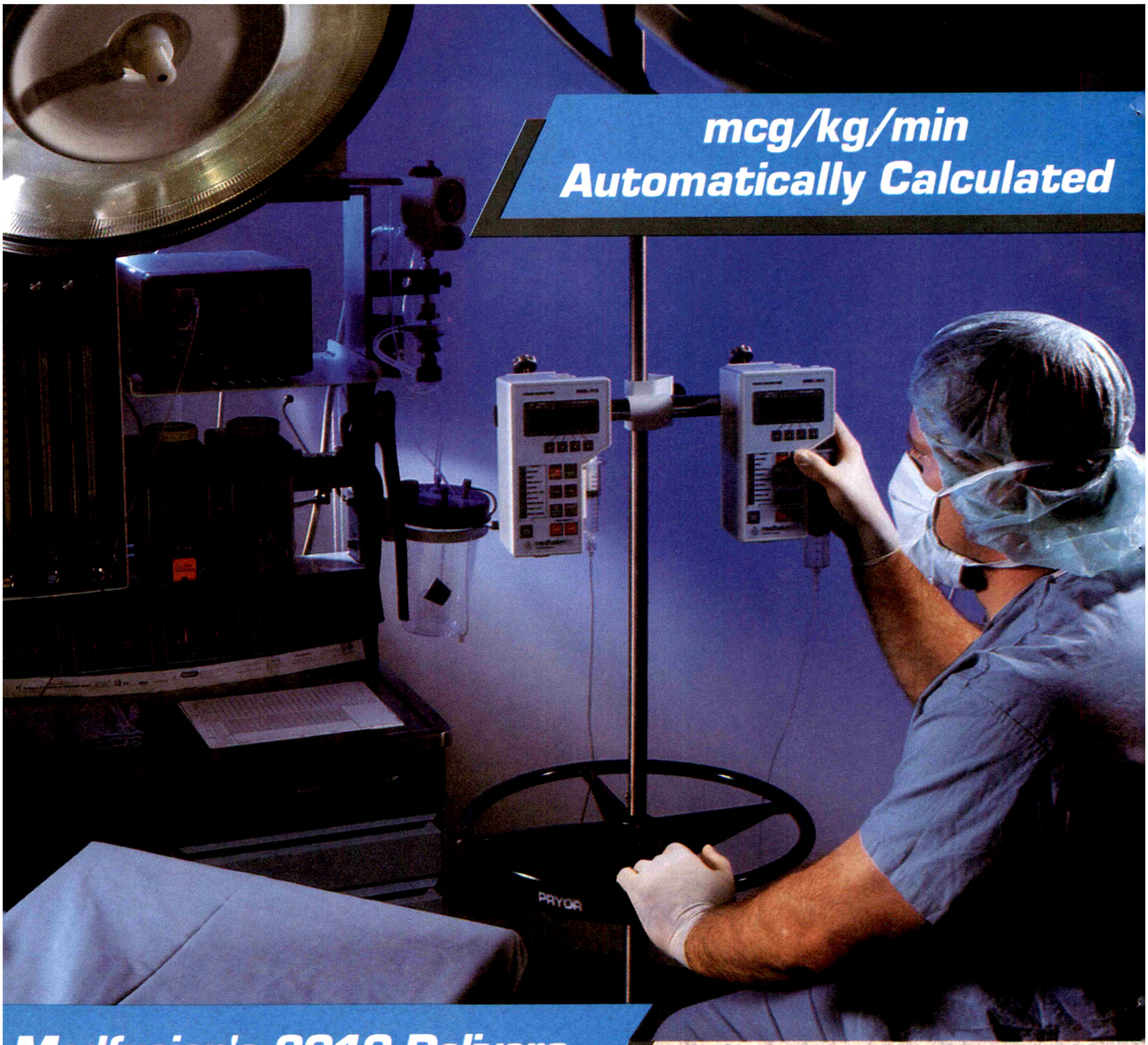

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This journal is abstracted/indexed in: Biological Abstracts, Chemical Abstracts, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Current Contents/Life Sciences, Current Contents/Clinical Practice, Excerpta Medica, Index Medicus, ISI/Biomed, and Science Citation Index.

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HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur.[1-4]	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma)[5]
RECOVERY To 25% of control To 95% of control	 25–45 min[3] 45–65 min[3]	 35–45 min[5] 60–70 min[5]
DOSING FLEXIBILITY	The initial recommended dose is 0.08–0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects.[1,3,4]	Initial recommended dose is 0.4–0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P<.05$) and 0.6 mg/kg.*[2,5,6]
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.† Can be reconstituted with various IV solutions including Lactated Ringers.‡	2-year shelf life under constant refrigeration.† Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated.[5]

*Dose of atracurium above 0.5 mg/kg is not recommended.
†As originally supplied by the respective manufacturers.
‡Storage after reconstitution varies with solution. See package insert.

Norcuron®

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.

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Norcuron®

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Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.
WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.
PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.
Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.
Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.
Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.
Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.
Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.
Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.
C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.
Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.
Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.
Drug/laboratory test interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.
Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.
Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.
ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.
OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.
DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.
Use by Continuous Infusion: After an intubating dose of 80-100 μg/kg, a continuous infusion of 1 μg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 μg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 μg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (μg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution
†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
μg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.
COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
STORAGE: 15-30°C (59-86°F). Protect from light.
AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

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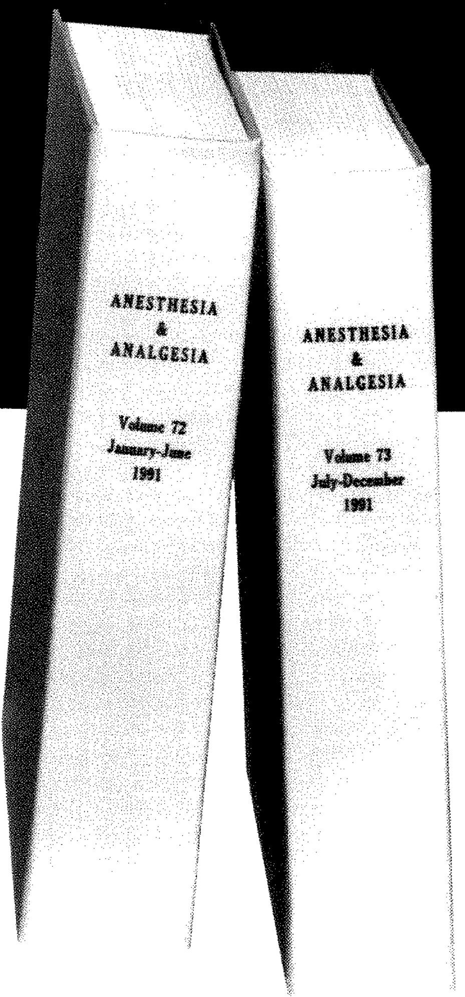

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EDITORIALS

Why Do "Pure" Vasodilators Cause Coronary Steal When Anesthetics Don't (or Seldom Do)?

Steven L. Lillehaug, MD, and John H. Tinker, MD

Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa

Adenosine is a remarkably effective "pure" arteriolar vasodilator. Recently it has been released in commercial form in the United States (Adenocard) for an extremely limited indication (i.e., as a bolus injection of 6–12 mg) to make use of another property, namely its well-known ability to slow artrioventricular conduction and perhaps to interrupt reentry mechanisms sufficiently to treat various types of paroxysmal supraventricular tachycardias, including those associated with Wolff-Parkinson-White syndrome. Its half-life is very short, ~10 s. It is obvious that the excellent arterial blood pressure control achievable with intravenous infusions of adenosine could lead to much wider application. Nitroprusside, our old standby for severe perioperative hypertension and deliberate intraoperative hypotension, has many drawbacks including difficult controllability, tachycardia, and potential for cyanide toxicity even in short-term infusions of more than 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (1). Hydralazine is not infusable, and reflex tachycardia can be a problem. Labetalol has gained recent popularity, but it is a "combination" drug, namely both an α- and β-adrenergic blocker, and is a relatively long-acting drug not suitable for infusion.

In this issue, Zäll et al. (2) reaffirm much that is already known about infusions of adenosine: when infused at rates of 60–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$, drug decreased mean arterial blood pressure and systemic and pulmonary vascular resistance and was associated with increased cardiac index, heart rate, and stroke volume without greatly affecting central filling pressures. Much the same has been reported earlier, particularly by another Swedish group, namely Owall et al. (3–5). Both Owall et al. (3,5) and now Zäll et al. report that adenosine produces marked increases in coronary flow without hemodynamic evidence of increased myocardial work.

In 1988, Owall et al. reported ". . . a moderate reduction in blood pressure by adenosine is associated with increased myocardial blood flow without increased myocardial oxygen utilization. The fact that one subject developed clear-cut ischemic ECG signs during the adenosine infusion warrants further studies into the effect of adenosine upon distribution of human coronary blood flow" (4). Owall et al. reported similar evidence of myocardial ischemia with adenosine in an earlier study in 1987 (3).

In this issue, Zäll et al. report myocardial ischemia with adenosine infusions in 6 to 14 patients who had two- or three-vessel coronary artery disease, but were studied during sternal closure *after* coronary artery bypass. Why did ischemia occur without evidence of increased myocardial work? Why do relatively "pure" arteriolar vasodilators such as nitroprusside (6), adenosine (7), and dipyridamole (8) cause coronary steal in various animal models and in humans, whereas the volatile anesthetic isoflurane, which is also clearly a coronary vasodilator, does not seem to do so. To be sure, in a dog model with a collateral-dependent myocardial zone with an artificially maintained constant coronary flow to mimic a "flow-limiting" stenosis at mean arterial blood pressures below 50 mm Hg, 1.0 MAC isoflurane did induce coronary steal (7). Also, there are anecdotes from human cases wherein ischemia developed during isoflurane and disappeared with the latter's discontinuance at similar arterial blood pressures and other hemodynamics. Nonetheless, the 1987 contention by Becker that isoflurane might be associated with steal in up to 50% of cases has not occurred (9). The large outcome studies of Tuman et al. (10) (1989—not randomized) and Slogoff and Keats (11) (1989—randomized) did not show that any particular anesthetic or technique, including isoflurane, was associated with any worsened cardiac outcome, including ischemia. Why not? Isoflurane *is* a coronary arteriolar dilator. Why doesn't it act like adenosine in this respect? Also, if the experimental volatile agent desflurane is to be added to our armamentarium, what are we to expect from it vis-à-vis coronary steal? Based on the large negative outcome studies (10,11),

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Accepted for publication August 26, 1991.

Address correspondence to Dr. Tinker, Department of Anesthesia, University of Iowa College of Medicine, Iowa City, IA 52242.

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0003-2999/91/$3.50

which made us breathe easier about isoflurane (sorry about the pun), we would not expect desflurane to be different. But it would be much better to *understand* the *mechanism* behind the fact that pure vasodilators like adenosine can cause a "steal" whereas vasodilatory anesthetics like isoflurane seldom do so.

Zäll et al. do not provide an answer. An obscure study (at least to anesthesiologists) by Gewirtz et al., published in *Circulation* in 1984, may provide a mechanism for the above important question. They developed a pig model of regional myocardial flow distribution and metabolism distal to a severe coronary stenosis and compared adenosine with nifedipine. As expected, adenosine resulted in decreased endocardial flow distal to the stenosis despite overall increased flow and decreased myocardial work (i.e., coronary steal). Regional lactate extraction was also decreased. In sharp contrast, when they used *nifedipine* to produce similar hemodynamics and overall coronary flow conditions, they saw a "decline in regional MVO_2, increased epicardial blood flow with variable effects on endocardial flow distal to the stenosis and no evidence of de novo or worsening ischemia, even in animals in which endocardial flow decreased" (12). Gewirtz et al. concluded that ". . . the extent of redistribution of flow and the metabolic consequences of coronary vasodilation distal to a severe coronary arterial stenosis may be influenced by the intrinsic negative inotrope effects of a drug used to produce vasodilation" (12).

This may explain why isoflurane, though a coronary dilator, seldom produces steal, namely because it also produces a negative inotropic effect. This may explain why we have few ischemic problems with nitroprusside during anesthesia, whereas it has certainly been implicated in the production of ischemia in the cardiology literature (6). Perhaps our negative inotropic anesthetics are acting similar to the negative inotropic properties of nifedipine in the study by Gewirtz et al. (12). Using this principle, one would doubt that labetalol, desflurane, or even pure arteriolar vasodilators used in combination with direct negative inotropes (e.g., anesthetics) would be associated very often with "steal."

Perhaps we can "get away" with use of adenosine as a replacement for nitroprusside if we happen also to have one or more negative inotropes "on board," but continued use postoperatively to control hypertension, a use which might otherwise be advocated because of the ease with which adenosine can be used to control arterial blood pressure, may cause ischemia in patients with coronary artery disease by a steal mechanism.

The study by Zäll et al., in which 6 of 14 patients experienced ischemia during sternal closure after coronary bypass, presumably after the most critical stenoses had been bypassed, should serve as a deterrent to those who may want to try adenosine in infusion form to treat perioperative hypertension and/or to produce deliberate intraoperative hypotension. To be sure, the FDA-approved indication is for supraventricular tachydysrhythmias only and in bolus injections only, but physicians are (and should be) permitted to use FDA-approved drugs for non-FDA-approved indications. This is not the place to discuss *that* complex and controversial issue! Perhaps we ought *not* to widen the usage of adenosine to control arterial blood pressure in many perioperative settings where it might seem like a good idea without (a) assurance that our patients could not possibly have coronary artery disease and (b) well-controlled studies. If the forerunner of the latter is that of Zäll et al., the future for adenosine as a vasodilator does not look good.

Finally, we submit that presence or absence of intrinsic negative cardiac inotropism may be the explanation for the fact that the pure vasodilators seem to be able to produce much more coronary steal than does isoflurane, despite the latter's similar ability to dilate coronary arteries.

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Epidural Anesthesia and Analgesia: Implications for Perioperative Coagulability

Susan M. Steele, MD, Thomas F. Slaughter, MD, Charles S. Greenberg, MD,
and J. G. Reves, MD

Departments of Anesthesiology and Medicine, Duke University Medical Center, Durham, North Carolina

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Epidural anesthesia and analgesia (EAA) has gained in popularity during the last 20 yr (1–3), in part because evidence has accumulated to support numerous physiologic benefits and superior pain relief. Whether combined general/epidural anesthesia with epidural analgesia continued into the postoperative period results in significant differences in outcome compared with general anesthesia alone remains controversial (4–6). The debate is in need of more and better data to support the opposing position. The study by Tuman et al. in this issue is welcome for it provides new evidence regarding the possible mechanism of the purported beneficial effects of EAA on postoperative morbidity in patients undergoing peripheral vascular surgery.

The concept of combining inhalational anesthesia and local infiltration with cocaine to block the nerve paths between the brain and the field of operation was described by Crile in 1910 (8). He coined the word "anoci-association," whereby combined inhalational and local anesthesia excludes the nervous system from all stimulation and perception of pain. Crile noted that for "fair-risk" patients anoci-association was not necessary; however, he suggested that the beneficial state of anoci-association in "handicapped" patients might be vitally important. In 1936, Odom administered epidural anesthesia in a series of 285 patients (9). He reported advantages of profound sensory anesthesia in patients thought to represent a poor operative risk. Odom concluded that epidural anesthesia could be used with safety in patients at increased risk for general anesthesia.

Users of perioperative EAA claim numerous beneficial effects resulting in improved outcome in specific patient populations. These effects include the following: amelioration of the neuroendocrine stress response to surgery (10); minimization of protein catabolism (11); improvement in pulmonary function by blunting the reduction in functional residual capacity (12,13); improvement in myocardial oxygen supply/demand ratios, cardiovascular stability, and global left ventricular function (14–16); enhancement of lower extremity and vascular graft blood flow (17); and finally a reduction in the thrombotic response to surgery (18). Epidural anesthesia and analgesia is associated with significant reductions in blood loss as well as reductions in cardiovascular, pulmonary, and infectious morbidity. Decreased thromboembolic complications have been described after orthopedic, urologic, and gynecologic surgeries performed with EAA. Most importantly, early mortality seems to be significantly reduced in patients undergoing hip surgery with regional anesthesia (5) and in high-risk patients undergoing thoracic, abdominal, and vascular surgery with EAA (4).

In this issue Tuman and colleagues (7) explore the effect of EAA on the coagulation system. Patients were randomized into two anesthetic groups receiving either general anesthesia alone or combined general/epidural anesthesia with epidural analgesia postoperatively. Despite the difficulty in trying to control for the multiplicity of factors affecting outcome in a heterogeneous patient population, the two groups appear comparable preoperatively and were confined to a single operative procedure, lower extremity revascularization. Postoperative intensive care was provided by independent caretakers unaware of the study goals, although obviously not blinded to treatment modality. Administration of a combined general/epidural anesthetic technique followed by continuous epidural analgesia resulted in shorter stays in the intensive care unit and significantly fewer cardiovascular and infectious complications, findings not unlike previous favorable outcome reports. What is new in this paper is the attempt to correlate the effect of epidural anesthesia on coagulation as determined by thromboelastographic measurements and clinical outcome on vascular graft patency. Despite the small differences between thromboelastographic measurements in the general and combined general/epidural

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Accepted for publication August 23, 1991.

Address correspondence to Dr. Steele, Department of Anesthesiology, Duke University Medical Center, Durham, NC 27710.

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0003-2999/91/$3.50

groups, an apparent improvement in vascular graft patency occurred in the group of patients selected to receive a combined general/epidural anesthetic.

Why might EAA improve graft patency? Based on previous studies of clinical outcome, epidural anesthesia appears to modify the postoperative thrombotic response. Measurement of coagulation activity during the postoperative period consistently demonstrates elevations of platelet reactivity, factor VIII, and von Willebrand factor (vWF). Antithrombin III, the principal inhibitor of thrombin activity, progressively decreases during the early postoperative period (19). An explanation for reduction in postoperative thrombotic complications in patients receiving epidural anesthesia remains to be determined, but we can speculate. Mechanisms may include epidural-mediated alterations in blood flow, as well as stress hormone and vWF concentrations. Epidural anesthesia increases blood flow to both calf and femoral veins (20,21). The stress-mediated release of cortisol, catecholamines, corticotropin, antidiuretic hormone, and numerous other metabolic precursors is blunted by high levels of epidural anesthesia (22). Von Willebrand factor, a large glycoprotein synthesized by the endothelium and megakaryocytes, is essential for the attachment of platelets to the vascular wall. Activation of endothelial cells or platelets, as occurs with vascular injury, releases vWF, possibly contributing to intravascular thrombosis (23). Local anesthetics decrease in vitro as well as in vivo platelet reactivity (24,25). In addition, epidural anesthesia limits the postoperative increases of both factor VIII and vWF (26). Antithrombin III returns to preoperative concentrations more rapidly in patients receiving epidural local anesthetics (27).

Tuman et al. used thromboelastography as a qualitative measurement of coagulation. The advantage of thromboelastography is its global assessment of coagulation from early fibrin formation to clot retraction. Thromboelastography offers the potential for the early detection of perioperative coagulopathies; however, the lack of standardization and of criteria defining a hypercoagulable state limits more widespread applications of this instrument. Based on thromboelastography measurements, the vascular patients in this study are hypercoagulable compared with a "healthy" population. Without quantitative measurements of coagulation proteins, we can only speculate as to an explanation. Fibrinogen, a glycoprotein essential to hemostasis and blood viscosity, is frequently increased in patients with vascular disease (28). Perhaps EAA reduces fibrinogen.

In conclusion, the paper by Tuman et al. (7) reemphasizes and supports the earlier findings in Yeager et al. (4). The improvement in vascular graft patency is interesting and deserves more investigation into the mechanism by which EAA produces this result. As epidural anesthesia and analgesia are labor intensive and expensive, outcome data supporting its benefit are not only welcome but necessary.

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Cardiac Dysrhythmias in Pediatric Patients During Anesthesia and the Role of Oximetry and Capnography

Paul R. Hickey, MD

Department of Anesthesiology, The Children's Hospital, Boston, Massachusetts

Because cardiac dysrhythmias are uncommon during anesthesia in children without known heart disease, their occurrence and persistence often present a management problem for the pediatric anesthesiologist. The information provided by Drs. Rolf and Coté (1) in this issue illuminates the etiology of pediatric dysrhythmias during anesthesia. By elucidating circumstances in which dysrhythmias commonly occur in children during anesthesia, some potentially helpful guides for their management resulted. The authors also suggest that the availability of oximetry and capnography data does not influence the incidence of dysrhythmias in children during anesthesia, dispelling some commonly held misperceptions about the genesis of dysrhythmias in anesthetized children.

However, to appreciate fully the importance of these data, the present paper (1) must be read in conjunction with an analysis of data from this same study previously published in *Anesthesiology* that focused on the utility of pulse oximetry and capnography in children during anesthesia (2). These two papers, taken together, strongly support the notion that routine oximetry and capnography are necessary during pediatric anesthesia because potentially deleterious levels of hypercapnia and hypoxemia in children usually *are not* accompanied by circulatory depression, and particularly not by dysrhythmias, until cardiovascular collapse occurs.

The striking findings in the analysis by Rolf and Coté are (a) lack of dysrhythmias in all 153 children less than 2 yr old, (b) lack of any relationship between arterial hemoglobin desaturation measured by pulse oximetry and occurrence of dysrhythmias, and (c) the virtual absence of dysrhythmias and lack of association with hypercapnia in tracheally intubated children versus a higher incidence of dysrhythmias and moderate association with hypercapnia in patients whose airways were managed via a mask. These findings deserve comment.

None of the 153 children less than 2 yr old in this study experienced dysrhythmias. In interpreting these data, the authors have attributed the absence of dysrhythmias to young age alone and have suggested several protective mechanisms that might be operative. Less marked myocardial sensitization to catecholamines by halothane in children is one mechanism cited, but the studies reporting this phenomenon did not study children less than 2 yr old nor suggest age-related differences in children as a group. The other suggestion that faster repolarization and shorter action potentials characterizing the electrical activity in the immature myocyte of the infant might protect against reentrant dysrhythmias is somewhat more appealing. However, this protective mechanism would be operative against some types of dysrhythmias but not against others. As the authors did not analyze the types of dysrhythmias that occurred in the study and their relative incidence, this potential protective mechanism is difficult to evaluate. It is unfortunate that such an analysis was not included in the present paper as it would give the practitioner a better sense of the probable etiology of dysrhythmias occurring during anesthesia in children and their relative importance.

The authors did not mention the relative paucity of sympathetic innervation of the immature heart, including decreased myocardial catecholamine stores and decreased arborization of sympathetic nerve endings. Functional sympathetic innervation of the heart is incomplete in a number of animal species for several months after birth (3). Although the timing in the human infant is not well studied, development of sympathetic innervation probably takes 6–12 mo or more to reach adult levels, helping to explain the absence of dysrhythmias in children less than 2 yr old. The authors' definition of dysrhythmias might also explain their absence in this age group. Sinus bradycardia was not considered as a dysrhythmia in their analysis, yet the most frequent terminal cardiac electrical activity in pediatric patients is bradycardia

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Accepted for publication July 30, 1991.

Address correspondence to Dr. Hickey, Department of Anesthesiology, The Children's Hospital, 300 Longwood Avenue, Boston, MA 02115.

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0003-2999/91/$3.50

(4). Sinus bradycardia may be a more sensitive indicator of hypoxemia than the dysrhythmias defined by the authors, and if considered as a dysrhythmia, it might have altered the results.

Additionally, no data are provided in these young children about the incidence of risk factors for dysrhythmias that were identified in the older children. Tracheal intubation was protective against dysrhythmias in this study and the tracheally intubated patients tended to be younger, so presumably those less than 2 yr old had a substantially greater incidence of intubation and were less at risk for dysrhythmias on this basis. No information on the incidence of light anesthesia, hypercapnia, or major desaturation events is presented for this age group in the present analysis, so whether the young children were more or less at risk from these potential factors also is not apparent. The previous analysis (2) suggests that infants less than 6 mo old had significantly more desaturation events and more "capnographic events" (? hypercapnia). To the limited extent that these are risk factors for dysrhythmias, the infant group might be somewhat more at risk. The incidence of light anesthesia in the young children studied is not given, thus the impact of this risk factor considered important by the authors is unknown. So although children under 2 yr of age were less at risk for dysrhythmias in this study, it is unclear whether this is due to their cardiac physiology, to a lower incidence of risk factors in this age group, or to both.

The lack of association between dysrhythmias and arterial desaturation episodes is clear in the data, but it is not emphasized in the discussion of the data. The authors stated in their results that none of the detected episodes of dysrhythmia in the older children were associated with hemoglobin desaturation. In the previously published analysis of these data (2), major desaturation events were significantly more frequent in the infant age group that had no episodes of dysrhythmias, so that despite a relatively higher incidence of desaturation in infants, dysrhythmias did not occur. This shows clearly that severe hypoxemia occurs for at least brief periods of time in small children without causing dysrhythmias or other clinically apparent cardiovascular changes. These findings emphasize the need for pulse oximetry in the early detection of hypoxemia in children if cardiovascular sequelae are to be avoided.

Lastly, virtual absence of dysrhythmias in tracheally intubated patients and the weak association between hypercapnia and dysrhythmias deserve comment. In patients whose tracheas were intubated, only 1 in 20 episodes of hypercapnia were associated with a dysrhythmia. The tracheally intubated child with the highest end-tidal CO_2, 85 mm Hg, did not develop a dysrhythmia. These findings emphasize that dysrhythmias cannot be relied on to occur in the presence of hypercapnia in tracheally intubated patients and that capnography is needed for its detection. It corroborates the classic (and ethically unrepeatable) study of apneic oxygenation in humans by Frumin et al. (5). In that classic study, anesthetized, tracheally intubated healthy adults were paralyzed and were left apneic with their endotracheal tubes connected to 100% oxygen. Apnea was allowed to continue for 30–55 min and pH values of 6.72–6.97 and arterial carbon dioxide tensions of 130–260 mm Hg were documented. Despite these extremes of acidosis and hypercapnia, only two of eight anesthetized, intubated patients developed dysrhythmias, forcing termination of their apnea. Cardiac dysrhythmias did not develop in the other six apneic patients.

Clearly, dysrhythmias cannot be relied on to signal the presence of extreme hypercapnia and acidosis in anesthetized, intubated adults and the study by Rolf and Coté suggests that this is also true in children. Even in the patients whose airways were managed via a mask in which the relationship between hypercapnia and dysrhythmia was stronger (9 of 16 hypercapneic episodes), a substantial proportion (44%) of the hypercapneic episodes that occurred were not associated with dysrhythmias. Although the authors advance several possible explanations for the much higher incidence of dysrhythmias in children whose airways were managed via a mask, the reason for the association remains unclear.

Taken together, these two papers advance our knowledge of the etiology of dysrhythmias in children during anesthesia and also strongly support the notion that routine oximetry and capnography are necessary during pediatric anesthesia. Potentially deleterious levels of hypercapnia and hypoxemia in children usually are not accompanied by clinically detectable levels of circulatory depression, and particularly not by dysrhythmias, until cardiovascular collapse occurs. Clearly, early detection of hypoxemia and hypercapnia in children is provided only by pulse oximetry and capnography. This is particularly true in young infants who are at considerably higher risk in Rolf and Coté's study and other studies for intraoperative hypoxemia and hypercapnia. Whether early detection of these problems improves clinical outcome by lowering major morbid complications and death in anesthetized children is a critically important question raised, but not answered, in either of the two published analyses of this important study.

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CARDIOVASCULAR ANESTHESIA
Section Editor
Joseph G. Reves

Effects of Adenosine on Myocardial Blood Flow and Metabolism After Coronary Artery Bypass Surgery

S. Zäll, MD, I. Milocco, MD, PhD, and S-E. Ricksten, MD, PhD

Department of Anesthesia and Intensive Care, Sahlgren's Hospital, University of Gothenburg, Gothenburg, Sweden

The effects of adenosine on myocardial blood flow and metabolism, central hemodynamics, and the intrapulmonary shunt fraction were investigated. Fourteen patients with two- or three-vessel coronary artery disease and with an ejection fraction greater than 0.5 were studied in the operating room following sternal closure after elective coronary artery bypass grafting. Systemic and pulmonary hemodynamics and global (coronary sinus), as well as regional myocardial blood flow (great cardiac vein flow), and metabolic variables were measured. Adenosine was given in infusion rates of 15, 30, 60, and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Infusion rates of 60 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ decreased mean arterial blood pressure (11% and 16%, respectively), systemic vascular resistance index (30% and 43%), and pulmonary vascular resistance index (24% and 31%), increased cardiac index (25% and 45%), heart rate (14% and 15%), and stroke volume index (9% and 25%), and had no effect on central filling pressures. These infusion rates doubled the intrapulmonary shunt fraction and decreased arterial O_2 tension by 26%. Great cardiac vein flow and coronary sinus flow increased 60% with adenosine infusion of 30–60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 120% with 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The ratio of great cardiac vein flow to coronary sinus flow, regional myocardial oxygen consumption, and mean regional lactate extraction and uptake were not significantly altered by adenosine. Adenosine caused a significant depression of the ST segment at infusion rates of 60 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In six patients, at infusion rates of 30–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$, adenosine caused or aggravated myocardial ischemia. We conclude that adenosine infusion after coronary artery bypass grafting induces systemic, pulmonary, and coronary vasodilation, increases the intrapulmonary shunt fraction, and may cause myocardial ischemia.

(Anesth Analg 1991;73:689–95)

Adenosine, a metabolic breakdown product of adenosine triphosphate, is a potent endogenous coronary vasodilator that may alter local regulation of coronary blood flow (1,2). In humans, adenosine-induced hypotension during anesthesia and surgery causes a pronounced coronary vasodilation (3,4). Nonhypotensive doses of adenosine increase peroperative coronary graft flow by 80%–90% with only minor effects on central hemodynamic variables (5). Perioperative and postoperative exogenous low-dose adenosine infusions may be beneficial with respect to postoperative coronary graft patency (5,6), as coronary artery grafts more frequently become occluded during the postoperative period when low graft flow values are obtained during and after surgery (7). However, unfavorable coronary redistribution of blood within the myocardium, or coronary steal, has been demonstrated with adenosine (8–10) in animal models of coronary artery disease. Furthermore, adenosine-induced hypotension may cause electrocardiographic signs of myocardial ischemia in some patients with a history of coronary artery or peripheral vascular disease (3,4).

The aim of the present investigation was, therefore, to study the effects of incremental doses of intravenous infusions of adenosine on myocardial blood flow and metabolism shortly after coronary artery bypass grafting and to evaluate whether adenosine in this situation may induce myocardial ischemia.

Methods

Fourteen patients (10 men and 4 women), with a mean age of 58.9 yr (range 40–69 yr), scheduled for elective coronary artery bypass surgery, were included in the study after informed consent was obtained. The study was approved by the Human

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This study was supported by grants from the Swedish Medical Research Council (No. 08682) and was presented in part at the annual meeting of the European Association of Cardiothoracic Anesthesiologists in Uppsala, Sweden, June 1989.

Accepted for publication July 1, 1991.

Address correspondence to Dr. Ricksten, Department of Anesthesia and Intensive Care, Sahlgren's Hospital, S-413 45 Gothenburg, Sweden.

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0003-2999/91/$3.50

Ethical Committee of the University of Gothenburg. All patients had two- or three-vessel coronary artery disease, with a mean ejection fraction of 0.65 (range 0.59–0.75). All patients were being treated with β-adrenergic receptor blockers preoperatively, which were continued until the morning of surgery.

Preanesthetic medication consisted of 0.1 mg/kg of intramuscular morphine and 0.4 mg of scopolamine. Anesthesia was induced with 3–5 mg/kg of thiopental, followed by 0.1 mg/kg of pancuronium to facilitate tracheal intubation, and continued with a combination of fentanyl (20 μg/kg), nitrous oxide (50%), and intermittent administration of a volatile anesthetic before cardiopulmonary bypass.

Pulmonary arterial (through the right subclavian vein) and radial arterial catheters were inserted for continuous recording of pulmonary and systemic arterial pressures. A three-thermistor regional coronary sinus catheter was inserted through the right internal jugular vein using a Seldinger technique under fluoroscopic guidance and continuous pressure monitoring. It was placed with its distal mixing thermistor in the great cardiac vein and its proximal mixing thermistor in the common coronary sinus, approximately 2 cm from the coronary sinus ostium. The appropriate position of the sinus catheter was confirmed by injection of 3–4 mL of contrast medium under fluoroscopy and by rapid central venous injection of cold saline during continuous flow recording.

Systolic, diastolic, and mean arterial (MAP) pressures were measured throughout the study as were systolic pulmonary, diastolic pulmonary, mean pulmonary arterial, pulmonary capillary wedge, and central venous pressures. Electrocardiogram lead V_5 was continuously monitored, together with pulmonary and systemic pressures on the Siemens Elema Sirecust Monitoring System. A continuous ST segment analysis was performed throughout the experimental procedure. The ST segment was evaluated 80 ms after the J point. Blood samples for lactate and oxygen content were drawn simultaneously from the great cardiac vein and systemic arteries. Blood oxygen tension and hemoglobin oxygen saturation were determined and lactate concentration was assayed using an enzymatic method (Lactate Analyser 640; Roche Bio-Electronics, Switzerland). Cardiac output was determined in triplicate by the thermodilution technique. Great cardiac vein flow (GCVF) and total coronary sinus flow (CSF) were determined by the retrograde thermodilution technique originally described by Ganz et al. (11) and modified by Pepine et al. (12). Normal saline at room temperature was used as the indicator and was injected at 40 mL/min over approximately 20 s. Changes in thermistor resistance owing to temperature changes were measured with a Wheatstone bridge. Cardiac index, stroke volume index, systemic and pulmonary vascular resistance indexes, and regional (great cardiac vein) myocardial oxygen consumption were calculated using the standard formula. The ratio of MAP to heart rate (HR) was calculated at each infusion rate of adenosine. Regional myocardial lactate extraction (RMLE) was calculated using the formula: RMLE = (arterial lactate − great cardiac vein lactate/arterial lactate) × 100. Regional myocardial lactate uptake (RMLU) was calculated as follows: RMLU = (arterial lactate − great cardiac vein lactate) × GCVF. Coronary perfusion pressure was defined as the mean diastolic pressure. The GCVF/CSF ratio was calculated. The intrapulmonary shunt fraction (Q_s/Q_t) was calculated using the formula $Q_s/Q_t = Cco_2 - Cao_2/Cco_2 - Cvo_2$, where Qs/Qt is venous admixture, Cco_2 is oxygen content in pulmonary end-capillary blood, Cao_2 is oxygen content of arterial blood, and Cvo_2 is oxygen content of mixed venous blood.

Myocardial ischemia was defined as a 0.1 mV or more depression of the ST segment, 0.2 mV or more increase in the ST segment, or regional myocardial lactate production. Adenosine-induced aggravation of myocardial ischemia was defined as a further depression of the ST segment of ≥0.1 mV or a further decrease in RMLU (arbitrary limit: >20 μmol/min) compared with control.

The experimental procedure started after sternal closure in the operating room. The patients' mean rectal temperatures were the same immediately before and after the experimental procedure (34.9 ± 0.4°C). The hematocrit was 27.2% ± 1.1% compared with a preoperative value of 39.7% ± 1.0%. Adenosine infusion rates of 15, 30, 60, and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were used in increasing order. Hemodynamic measurements and blood samples were obtained after 5 min of infusion at each infusion rate. Values before the start of adenosine infusion were considered as control values. Five minutes after discontinuation of the highest infusion rate, final measurements were performed. The duration of the experimental procedure was thus 30–35 min. The patients were normoventilated with 50% nitrous oxide in oxygen. Volatile anesthetics were not administered after cardiopulmonary bypass and no fentanyl and no fluid were given during the experimental procedure. All results are reported as mean ± SEM. Data were analyzed using a one-way analysis of variance for repeated measurements followed by Dunnet's multiple range test (13).

Results

Data on systemic and pulmonary hemodynamics are given in Table 1, and data on coronary hemodynamics and metabolism are given in Table 2. Individual data on

Table 1. Hemodynamic Effects of Adenosine

	Adenosine infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)					
	0	15	30	60	120	0
SAP (mm Hg)	123.7 ± 3.1	118.7 ± 4.0	120.2 ± 4.2	112.2 ± 5.2^a	107.0 ± 5.8^a	125.4 ± 5.3
MAP (mm Hg)	88.7 ± 2.0	86.0 ± 2.5	89.5 ± 2.4	79.1 ± 3.5^a	74.5 ± 3.8^a	91.6 ± 3.2
DAP (mm Hg)	68.8 ± 1.8	67.9 ± 1.6	69.4 ± 2.2	59.8 ± 2.7^a	55.8 ± 3.0^a	70.2 ± 2.1
SPAP (mm Hg)	28.9 ± 1.2	27.4 ± 1.3	26.7 ± 1.2	28.3 ± 1.2	29.4 ± 1.4	31.0 ± 1.3
MPAP (mm Hg)	20.8 ± 1.0	19.4 ± 1.0	18.9 ± 1.0	20.3 ± 0.9	20.6 ± 1.0	21.1 ± 0.8
DPAP (mm Hg)	14.7 ± 1.0	13.5 ± 1.1	13.2 ± 0.9	13.7 ± 0.9	14.1 ± 0.9	13.6 ± 0.8
CVP (mm Hg)	11.0 ± 1.0	10.1 ± 0.8	10.1 ± 0.7	11.6 ± 0.8	11.4 ± 0.7	10.9 ± 0.6
PCWP (mm Hg)	13.1 ± 1.1	11.6 ± 0.9	11.7 ± 0.8	12.7 ± 0.8	12.8 ± 0.7	12.6 ± 0.7
SVRI (mm $Hg \cdot L^{-1} \cdot min \cdot m^2$)	41.9 ± 3.0	43.0 ± 2.3	40.3 ± 2.7	29.3 ± 2.6^a	23.7 ± 1.9^a	39.9 ± 2.8
PVRI (mm $Hg \cdot L^{-1} \cdot min \cdot m^2$)	4.2 ± 0.4	4.5 ± 0.5	3.7 ± 0.4	3.2 ± 0.4^a	2.9 ± 0.3^a	4.2 ± 0.3
HR (beats/min)	65.0 ± 2.6	64.6 ± 2.2	67.1 ± 2.5	74.3 ± 2.8^a	74.9 ± 2.7^a	70.6 ± 3.1^b
SVI (mL/m^2)	30.7 ± 2.1	28.8 ± 1.8	31.6 ± 1.9	33.4 ± 2.2	38.5 ± 3.3^a	30.8 ± 2.1
CI (L/m^2)	2.0 ± 0.1	1.9 ± 0.2	2.1 ± 0.2	2.5 ± 0.2^a	2.9 ± 0.3^a	2.2 ± 0.2
Intrapulmonary shunt (%)	10.7 ± 2.0	11.2 ± 1.6	13.0 ± 2.3	18.1 ± 1.7^a	20.0 ± 1.7^a	9.6 ± 1.1
Pa_{O_2} (mm Hg)	120.3 ± 13.8	120.0 ± 11.6	111.7 ± 9.5	88.7 ± 8.0^a	89.9 ± 10.2^a	122.2 ± 10.7

SAP, systolic arterial pressure; MAP, mean arterial pressure, DAP, diastolic arterial pressure; SPAP, systolic pulmonary arterial pressure; MPAP, mean pulmonary arterial pressure; DPAP, diastolic pulmonary arterial pressure; CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; HR, heart rate; SVI, stroke volume index; CI, cardiac index; Pa_{O_2}, arterial oxygen tension.

Values are mean ± SEM ($n = 14$).

[a] $P < 0.01$, control vs 15, 30, 60, 120, and 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

[b] $P < 0.05$, control vs 15, 30, 60, 120, and 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Table 2. Effects of Adenosine on Coronary Hemodynamics and Metabolism, Atrioventricular Conduction Time, and ST Segment

	Adenosine infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)					
	0	15	30	60	120	0
CPP (mm Hg)	81.4 ± 3.1	79.7 ± 2.3	80.0 ± 2.6	70.6 ± 3.4^a	62.1 ± 3.1^a	83.4 ± 2.6
CSF (mL/min)	212.0 ± 32.6	215.5 ± 35.8	283.7 ± 42.1	339.6 ± 53.2^a	469.6 ± 89.9^a	237.1 ± 42.5
GCVF (mL/min)	85.2 ± 2.2	88.1 ± 15.6	139.2 ± 26.9^b	187.5 ± 31.5^a	176.0 ± 39.4^a	111.7 ± 22.6
GCVF/CSF ratio	0.44 ± 0.05	0.43 ± 0.07	0.49 ± 0.08	0.55 ± 0.08	0.41 ± 0.06	0.48 ± 0.06
$CGCV_{O_2}$ (mL/100 mL)	62.1 ± 4.0	64.8 ± 4.6	88.1 ± 5.0^a	99.8 ± 5.1^a	101.6 ± 6.8^a	73.3 ± 5.2^b
RMV_{O_2} (mL/min)	6.2 ± 0.9	5.8 ± 0.7	5.6 ± 0.9	6.1 ± 0.9	5.4 ± 1.1	6.3 ± 0.6
RMLE (%)	−6.7 ± 6.6	−11.3 ± 7.5	−9.8 ± 6.0	−8.2 ± 2.9	−8.9 ± 6.9	−3.2 ± 6.7
RMLU (μmol/min)	−2.9 ± 2.6	−6.9 ± 3.9	−7.2 ± 4.3	−14.0 ± 5.8	−14.9 ± 13.1	−0.7 ± 3.0
PR interval (s)	0.101 ± 0.005	0.101 ± 0.005	0.105 ± 0.005	0.107 ± 0.005^a	0.109 ± 0.005^a	0.100 ± 0.005
ST seg depr (mV)	−0.008 ± 0.025	−0.008 ± 0.025	−0.014 ± 0.025	−0.046 ± 0.027^a	−0.058 ± 0.028^a	−0.019 ± 0.021

CPP, coronary perfusion pressure; CSF, coronary sinus flow, GCVF, great cardiac vein flow; $CGCV_{O_2}$, great cardiac vein oxygen content; RMV_{O_2}, regional myocardial oxygen consumption; RMLE, regional myocardial lactate extraction; RMLU, regional myocardial lactate uptake; PR interval, PR interval time; ST seg depr, ST segment depression.

Values are mean ± SEM ($n = 14$).

[a] $P < 0.01$, control vs 15, 30, 60, 120, and 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

[b] $P < 0.05$, control vs 15, 30, 60, 120, and 0 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

regional myocardial lactate extraction and uptake are given in Table 3, and individual data on ST segment deviation and the MAP/HR ratio are given in Table 4.

Systemic Hemodynamics

Adenosine infusion rates of 15–30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ caused no significant alterations in systemic hemodynamics. A rate of 60–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ induced a 10%–15% decrease in systolic arterial pressure, diastolic arterial pressure, and MAP due to systemic vasodilation with a decrease in systemic vascular resistance index (30% and 43%, respectively). The increase in cardiac index was caused by a 14% increase in HR at 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and with increases in both HR (15%) and stroke volume index (25%) at 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Central venous pressure was unaffected during all adenosine infusion rates.

Table 3. Individual Data on the Effects of Adenosine on Regional Myocardial Lactate Extraction and Uptake

	Adenosine infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)											
	0		15		30		60		120		0	
Patient	RMLE	RMLU	RMLE	RMLU	RMLE	RMLU	RMLE	RMLU	RMLE	RMLU	RMLE	RMLU
1	10	6	−4	−6	−2	−5	−5	−11	−5	−11	−2	−4
2	5	6	2	3	−14	−20	−13	−22	−18	−29	−2	−3
3	8	4	−16	−8	−13	−7	−10	−2	−34	−13	−22	−7
4	−3	−5	−7	−16	−2	−8	−18	−83	−27	−161	−1	−3
5	−13	−12	−13	−11	−63	−54	−9	−15	−15	−14	−11	−8
6	−86	−21	−97	−46	−55	−16	−37	−21	−64	−21	−69	−19
7	25	14	28	19	18	17	2	3	6	6	22	12
8	−3	−1	0	0	0	0	6	1	8	4	4	2
9	−7	−9	−2	−2	0	0	−4	−8	—	—	0	0
10	−6	−3	−23	−10	−8	−5	−13	−10	−11	−6	−4	−2
11	−2	−1	−1	−1	2	2	−8	−18	−4	−6	0	0
12	−11	−8	−23	−15	−5	−4	−4	−3	3	3	−1	1
13	−17	−16	−10	−8	−6	−7	−8	−12	3	8	−7	−7
14	5	4	7	4	10	6	5	6	42	46	49	31

RMLE, regional myocardial lactate extraction (%); RMLU, regional myocardial lactate uptake (μmol/min).

Table 4. Individual Data on the Effects of Adenosine on ST Segments and Ratios of Mean Arterial Pressure to Heart Rate

	Adenosine infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)											
	0		15		30		60		120		0	
Patient	ST	MAP/HR	ST	MAP/HR	ST	MAP/HR	ST	MAP/HR	ST	MAP/HR	ST	MAP/HR
1	±0	1.37	±0	1.33	±0	1.20	−0.05	1.11	−0.1	0.96	−0.05	1.23
2	−0.15	1.28	−0.15	1.19	−0.2	1.15	−0.25	0.78	−0.25	0.78	−0.15	1.31
3	±0	1.76	±0	1.37	±0	1.47	−0.05	1.18	−0.05	0.94	±0	1.26
4	—	1.07	—	1.21	0.1	1.06	0.1	1.01	0.1	0.98	0.1	1.11
5	0.15	1.39	0.15	1.13	0.1	1.17	—	1.08	—	1.05	—	1.05
6	±0	1.51	±0	1.62	−0.05	1.66	−0.15	1.46	−0.15	1.06	−0.05	1.72
7	±0	1.02	±0	1.30	±0	1.23	±0	0.91	±0	0.83	±0	1.29
8	±0	1.44	±0	1.47	±0	1.36	±0	0.90	±0	0.75	±0	1.09
9	−0.1	1.23	−0.1	1.25	−0.1	1.36	−0.1	0.96	−0.1	0.86	−0.1	1.21
10	±0	1.07	±0	1.29	−0.05	1.22	−0.05	1.23	−0.05	1.30	±0	1.54
11	±0	1.76	±0	1.49	±0	1.47	±0	1.14	±0	1.28	±0	1.40
12	−0.15	1.41	−0.15	1.49	−0.15	1.59	−0.15	1.02	−0.2	1.32	−0.15	1.53
13	±0	1.44	±0	1.36	±0	1.49	±0	1.41	±0	1.33	±0	1.67
14	0.15	1.56	0.15	1.23	0.15	1.19	0.1	0.87	0.05	0.78	0.1	1.44

ST, ST segment depression (mV); MAP/HR, mean arterial pressure/heart rate ratio.

Pulmonary Hemodynamics

Systolic pulmonary pressure, MPAP, diastolic pulmonary arterial pressure, and pulmonary capillary wedge pressure did not change during adenosine infusion. Pulmonary vascular resistance index decreased 24% and 31%, respectively, at infusion rates of 60 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. At the same doses of adenosine, the intrapulmonary shunt fraction increased and the arterial O_2 tension (Po_2) decreased significantly.

Coronary Hemodynamics and Metabolism

Great cardiac vein flow and CSF increased significantly by 30%–60% at an adenosine dose of 30–60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and by 120% at a dose of 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Great cardiac vein O_2 content increased dose-dependently at 30–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The GCVF/CSF ratio was not significantly altered by adenosine. Regional myocardial oxygen consumption, and RMLE as well as RMLU were not significantly changed by adenosine administration.

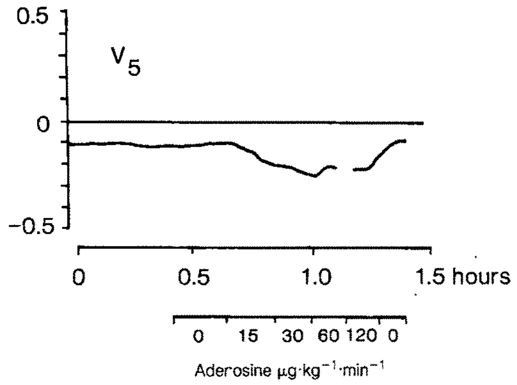

Figure 1. ST segment depression (V_5) in one patient (patient 2) during incremental infusion rates of adenosine.

In two patients (patients 4 and 5) the ST segment could not be evaluated at all infusion rates because of conduction abnormalities. Adenosine induced a significant depression of the ST segment at 60 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (Table 2). The PR interval increased significantly at 60 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Adenosine caused lactate production compared with RMLU uptake before adenosine infusion in patients 1, 2, and 3 (Table 3). This was accompanied by an adenosine-induced ST segment depression ≥0.1 mV in patients 1 and 2 (Figure 1) (Table 3). In patients 4 and 5, adenosine induced a more pronounced lactate release compared with control at doses of 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (patient 5) and 60–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (patient 4). In patient 6, adenosine induced an ST segment depression greater than 0.1 mV. In patients 7–13, adenosine caused an ST segment depression less than 0.1 mV with only minor changes in lactate metabolism (Tables 3 and 4). In patient 14, RMLU increased markedly at the highest infusion rate, which was associated with a normalization of the ST segment.

The mean values of the MAP/HR ratios for patients 1–6 were 1.10 ± 0.22 at 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.96 ± 0.1 at 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The corresponding values for patients 7–14 were 1.06 ± 0.19 and 1.06 ± 0.27, which did not differ significantly from values for patients 1–6.

Discussion

In the present study of patients studied shortly after coronary artery bypass grafting (CABG), incremental doses of adenosine (30–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$) induced a pronounced dose-dependent coronary vasodilation with a 60% increase in GCVF even at a nonhypotensive dose of 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$. These results are in line with data from a recent study by Torsell et al. (5), who measured flow in coronary artery bypass grafts by electromagnetic flow probes before closure of the thorax. They found that nonhypotensive doses of adenosine (30–50 $\mu g \cdot kg^{-1} \cdot min^{-1}$) increased graft flow by 84% without affecting left ventricular work. At the largest infusion rate of adenosine used in the present study (120 $\mu g \cdot kg^{-1} \cdot min^{-1}$), a 120% increase in CSF was seen, results that agree with those reported by Öwall et al. (3) who found that adenosine infusion at a rate of 90 $\mu g \cdot kg^{-1} \cdot min^{-1}$ induced a 130% increase in CSF in fentanyl-anesthetized patients with peripheral vascular disease.

Exogenous administration of adenosine in animals usually decreases HR (14), which, together with its afterload-reducing effect, decreases myocardial oxygen consumption (14–16). In the present study, adenosine infusion caused no change in regional myocardial oxygen consumption in spite of the reduction in left ventricular outflow impedance, which could be explained by the 15% increase in HR. This reflex increase in HR has previously been described by others during adenosine-induced hypotension (17), and thus may occur in humans in spite of the inhibitory effect of adenosine on sinus node automaticity (2,7,18) and its inhibitory effect on sympathetic nerves to the myocardium (7), as well as its counteracting effect on sympathoadrenal activation (3). Others have previously shown that adenosine-induced hypotension causes no change (3) or a moderate decrease (4) in myocardial oxygen demand in animals, a decrease that is less pronounced or absent in humans probably owing to its mild chronotropic effect.

Adenosine infusion induced a systemic vasodilation at the doses of 60 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$ while not affecting central filling pressures, indicating that adenosine dilates mainly resistance vessels and has no effect on venous capacitance vessels. These data support findings from previous work on the effects of adenosine on central hemodynamics during induced hypotension in patients undergoing cerebral aneurysm surgery (4,17). Furthermore, our findings support the suggestion by Sollevi (6) that adenosine might be used as an afterload-reducing compound in various forms of low cardiac output states.

More than 60% of our patients produced lactate in the area of the left anterior descending artery, drained by the great cardiac vein, before the start of adenosine infusion. In only two of these patients were there electrocardiographic signs of myocardial ischemia, which confirms the findings of Häggmark et al. (19), who showed little agreement between electrocardiographic and metabolic (lactate production) indices of myocardial ischemia. In two patients there was a pronounced increase in net lactate release associated with adenosine, whereas in another three patients not producing lactate during the control situation, adenosine caused lactate production. One could argue that the adenosine-induced impairment of myocardial lactate metabolism after cardiopulmonary bypass in these patients could be a "washout" effect caused by the pronounced increase in myocardial blood flow and not necessarily by myocardial ischemia. However, two patients with adenosine-induced lactate production also had ST segment depression greater than 0.1 mV. Furthermore, in another patient, adenosine induced clear-cut electrocardiographic signs of myocardial ischemia. Finally, adenosine induced a significant depression of the mean ST segment in patients given adenosine at infusion rates of 60 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

We chose a difficult time period to study the effects of adenosine on myocardial blood flow and metabolism after CABG. In the face of changing baseline conditions, as seen in most patients shortly after bypass, one could argue that the cardiometabolic, hemodynamic, and electrocardiographic changes seen during adenosine infusion cannot be regarded as entirely related to the adenosine administration, but rather to a gradual, time-dependent resolution of ischemia in some patients and worsening of ischemia in others. However, the duration of the experimental procedure was relatively short (30–35 min). Mean body temperature did not change and the patients did not receive any fluid or anesthetics during the study period. Furthermore, mean values of systemic, pulmonary, and coronary hemodynamics as well as arterial oxygenation, PR interval, and ST segment depression returned to control levels within 5 min after discontinuation of the highest dose of adenosine. It is therefore likely that the induction or aggravation of myocardial ischemia seen in patients 1–6 during the study period was associated with adenosine administration. These data could therefore be of clinical significance, especially as perioperative adenosine treatment may be useful in preventing early occlusion of coronary artery bypass grafts (5,7). What then are the mechanism(s) behind adenosine-induced myocardial ischemia shortly after CABG?

One obvious explanation for adenosine-induced myocardial ischemia in the present study could be the combination of a moderate increase in HR and decline in coronary perfusion pressure in the presence of recently grafted coronary arteries. The MAP/HR ratio may predict myocardial ischemia in animals (20,21) and humans (22). A decrease in the MAP/HR ratio below 1.0 is frequently associated with ischemia. At the largest dose of adenosine, almost 60% of the patients had MAP/HR ratios below 1.0. However, the mean MAP/HR ratio of patients 1–6, with metabolic and/or electrocardiographic signs of myocardial ischemia, was not significantly different from that of nonischemic patients (patients 7–14) at the largest doses of adenosine. Adenosine in animal models of coronary artery disease may cause myocardial ischemia owing to redistribution of flow ("coronary steal") (8–10). In the present study, the patients had undergone CABG with three to six peripheral anastomoses, which would render an intercoronary steal mechanism less likely even if the patients had a steal-prone coronary anatomy (23) before bypass. Furthermore, there was no significant change in the GCVF/CSF ratio, or in regional myocardial oxygen consumption, which would indicate that adenosine-induced coronary vasodilation was not associated with regional myocardial redistribution. However, one cannot exclude the possibility that adenosine in this situation may cause a transmural redistribution of blood flow, which cannot be detected by the retrograde coronary sinus thermodilution technique. It has been demonstrated in animals that there is a persistent vasodilatory reserve in the epicardium distal to a critical coronary stenosis and that intracoronary administration of adenosine may redistribute blood flow away from the endocardium distal to the stenosis, i.e., an intramural steal (24,25). One could also speculate that the surgical procedure was suboptimal in some patients in the present study (e.g., graft malfunction, residual stenosis not grafted) and that adenosine in these patients caused some form of flow maldistribution. In one patient, an elevated ST segment almost normalized during adenosine infusion, which was accompanied by a pronounced increase in RMLU. It is not evident whether this was caused by adenosine or a spontaneous resolution of ischemia.

Administration of vasodilators such as sodium nitroprusside and nitroglycerin to anesthetized patients to induce hypotension may result in a decrease in Pa_{O_2} (26). The mechanism behind this is a direct vasodilatory effect on the pulmonary vasculature causing inhibition of hypoxic vasoconstriction, which in turn increases the ventilation-perfusion abnormalities. In the present study, adenosine decreased pulmonary vascular resistance, while increasing intrapulmonary shunt fraction and decreasing Pa_{O_2}, suggesting that adenosine, like other vasodilators, also may inhibit pulmonary hypoxic vasoconstriction.

Atrioventricular nodal conduction time is prolonged by adenosine (2,18). In the present study there was a significant 6%–8% increase in the PR interval at a dose of 60 and 120 $\mu g \cdot kg^{-1} \cdot min^{-1}$, findings which agree with those reported by Öwall et al. (17). In no patient did adenosine induce an atrioventricular block.

In the present study on patients shortly after CABG, incremental doses of adenosine (15–120 $\mu g \cdot kg^{-1} \cdot min^{-1}$) induced dose-dependent decreases in MAP, systemic vascular resistance index, and pulmonary vascular resistance index accompanied by increases in HR, stroke volume index, and cardiac index, whereas central filling pressures remained unchanged. Adenosine also induced profound coronary vasodilation, even at a nonhypotensive dose of 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$, whereas myocardial oxygen demand was unchanged. In some patients, adenosine induced lactate production or induced more pronounced net lactate release associated with ST segment depression, indicative of regional myocardial ischemia. We conclude that low-dose adenosine infusion shortly after coronary artery bypass surgery may cause myocardial ischemia.

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Effects of Epidural Anesthesia and Analgesia on Coagulation and Outcome After Major Vascular Surgery

Kenneth J. Tuman, MD, Robert J. McCarthy, PharmD, Robert J. March, MD,
Giacomo A. DeLaria, MD, Rajesh V. Patel, MD, and Anthony D. Ivankovich, MD

Departments of Anesthesiology and Cardiovascular Surgery, Rush-Presbyterian-St. Luke's Medical Center,
Chicago, Illinois

To examine the interaction of epidural anesthesia, coagulation status, and outcome after lower extremity revascularization, 80 patients with atherosclerotic vascular disease were prospectively randomized to receive general anesthesia combined with postoperative epidural analgesia (GEN-EPI) or general anesthesia with on-demand narcotic analgesia (GEN). Demographics did not differ between groups except that the GEN-EPI group had a higher incidence of diabetes mellitus and of previous myocardial infarction. Coagulation status was monitored using thromboelastography. An additional 40 randomly selected patients without atherosclerotic vascular disease undergoing noncardiovascular procedures served as controls for coagulation status. Vascular surgical patients were hypercoagulable compared with control patients before operation and on the first postoperative day. Postoperatively, this hypercoagulability was attenuated in the GEN-EPI group and was associated with a lower incidence of thrombotic events (peripheral arterial graft, coronary artery or deep vein thromboses). The rates of cardiovascular, infectious, and overall postoperative complications, as well as duration of intensive care unit stay, were significantly reduced in the GEN-EPI group. Stepwise logistic regression demonstrated that the only significant predictors of postoperative cardiovascular complications were preoperative congestive heart failure and general anesthesia without epidural analgesia. We conclude that in patients with atherosclerotic vascular disease undergoing arterial reconstructive surgery (a) thromboelastographic evidence of increased platelet-fibrinogen interaction is associated with early postoperative thrombotic events, and (b) epidural anesthesia and analgesia is associated with beneficial effects on coagulation status and postoperative outcome compared with intermittent on-demand opioid analgesia.

(Anesth Analg 1991;73:696–704)

Patients with atherosclerosis who undergo major peripheral vascular surgery are at increased risk for postoperative cardiovascular complications (1–3). In a previous study by Yeager et al. (4), high-risk patients receiving combined epidural-general anesthesia for a variety of surgical procedures exhibited a significantly lower postoperative cardiovascular complication rate compared with general anesthesia alone. Currently, clinical application of these findings to high-risk vascular surgical patients has been limited by the small number of such patients in the Yeager et al. study and by the lack of confirmatory studies in this subset of patients. Verification of these rather striking findings in a larger sample of vascular surgical patients is necessary because of the potential impact on patient management (5). In addition, study of a more homogeneous surgical population allows examination of the interaction of anesthetic choice with other factors known to affect postoperative outcome.

Factors that may influence perioperative morbidity in these patients are advanced age, significant coronary artery disease, hypertension, congestive heart failure, and the stresses of peripheral vascular surgery itself. In addition, the hemostatic system is an important factor in atherosclerosis and its complications. Hypercoagulability manifested by increased fibrinogen and platelet activity has been implicated in the genesis of unstable angina, intracoronary thrombosis, and myocardial infarction (6,7). Patients undergoing peripheral vascular surgery have postoperative increases in platelet reactivity and in factor VIII-related antigen and have decreases in antithrombin III levels indicative of a hypercoagulable state that can be associated with early arterial graft failure (8,9).

Accepted for publication July 1, 1991.

Address correspondence to Dr. Tuman, Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, 1653 West Congress Parkway, Chicago, IL 60612.

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0003-2999/91/$3.50

These disease-related changes in coagulation may be exacerbated by surgical and postoperative stress (10).

As most cardiovascular morbidity occurs in the hours and days after completion of vascular surgery, postoperative stress-induced hypercoagulability could play a causal role. Epidural anesthesia and analgesia continuing into the postoperative period can attenuate the postoperative stress response in specific patient populations (4,11–13). Epidural anesthesia and analgesia is also associated with direct and indirect effects on the hemostatic system and may result in diminished postoperative hypercoagulability (14–16). If postoperative anesthetic management, such as the use of continuous epidural analgesia, positively influences outcome in high-risk patients in the hours and days after major peripheral vascular surgery, it may do so by altering the coagulation system.

With these considerations in mind, this study was designed to reevaluate the association of epidural-general anesthesia and postoperative epidural analgesia with improved cardiovascular and overall outcome after major vascular surgery. We also sought to study the previously untested hypothesis of an association between coagulation state, postoperative complications, and choice of anesthetic in high-risk vascular patients. An additional goal of this study was to determine the relative importance of anesthetic management compared with preoperative risk factors for adverse cardiovascular outcome in patients undergoing major peripheral vascular surgery.

Methods

Perioperative Management

With institutional review board approval, 80 consenting adults undergoing major vascular surgery of the abdominal aorta and lower extremities were randomly assigned to receive general anesthesia combined with epidural anesthesia and analgesia (GEN-EPI), or general anesthesia with postoperative parenteral and/or oral narcotic administration (GEN). Patients with preoperative coagulopathies or liver disease, receiving anticoagulant or antiplatelet medications, or with any contraindication to the use of an epidural catheter, or any of the standard anesthetic/analgesic agents employed, were excluded from entry into this study.

Intraoperatively, patients in the GEN group received an anesthetic consisting of inhaled nitrous oxide, oxygen, isoflurane ($\leq$1.5% inspired), and $\leq$15 μg/kg of intravenous fentanyl. Postoperatively, GEN patients received parenteral and/or oral narcotic analgesics as requested for pain relief. Patients in the GEN-EPI group had high lumbar or low thoracic (L-3–T-10) epidural catheters inserted using a standard loss of resistance technique before induction of general anesthesia. Epidural catheters were evaluated for accidental intravascular or intrathecal placement and for evidence of dermatomal spread (±1 spinal segment) of analgesia using a 3-mL test dose of lidocaine (1.5%) with epinephrine (1:200,000). Intraoperatively, the anesthesia for the GEN-EPI patients was maintained with inhaled nitrous oxide, low concentrations of isoflurane ($\leq$0.5% inspired), $\leq$5 μg/kg of intravenous fentanyl, and incremental injections of 1.5% lidocaine administered through the epidural catheter to achieve surgical anesthesia. After initial dosing with local anesthetic, the epidural catheter was redosed at the discretion of the anesthesiologist using approximately one-half of the original dose of local anesthetic if hemodynamic changes and the requirement for general anesthetic drugs suggested that the level of analgesia provided by the local anesthetic had decreased. The total volume of local anesthetic used intraoperatively (12–20 mL) was determined by analgesic and anesthetic requirements of the individual patient. Nondepolarizing muscle relaxants were used in both groups to facilitate control of ventilation, primarily during surgery of the abdominal aorta.

In the GEN-EPI group, a continuous epidural infusion of fentanyl (0.001%) and bupivacaine (0.1%) at 5–8 mL/h was initiated at least 30 min before anticipated completion of the surgical procedure. When necessary, parenteral narcotics were used to supplement pain relief, and the duration of postoperative epidural analgesia was a clinical decision not dictated by study protocol. Patients receiving epidural analgesia were evaluated at least daily by a member of the Department of Anesthesiology acute postoperative pain service, and care was given according to established pain service protocols.

The trachea was intubated, and ventilation was controlled, for at least the duration of the operation, in both anesthetic groups. In both groups, choice of premedication and specific doses of anesthetic and nonanesthetic agents were at the discretion of the anesthesiologist and depended on the patient's condition and the requirements for providing amnesia, muscle relaxation, and hemodynamic stability. Chronically administered cardiac medications were given on the morning of operation. All patients had monitoring of electrocardiographic leads II and V_5 and of intraarterial catheters for arterial blood pressure measurements and for analysis of blood gas tensions and hematocrit. All patients undergoing procedures involving the abdominal aorta had central venous catheters inserted in the operating room. During the perioperative period, hemodynamic aberrations exceeding 20% of baseline, serious dysrhythmias, and ischemia were treated.

Intraoperatively, all patients undergoing vascular clamping received 50–75 mg of heparin, reversed with protamine. No blood products except packed red blood cells were administered. Postoperatively, no patients received anticoagulants except for one patient in the GEN group who received a heparin infusion in the immediate postoperative period because of an acute vascular graft thrombosis.

Coagulation monitoring was performed using a commercially available thromboelastograph (BICLOT ELVI 816 Thromboelastograph, Logos Scientific, Henderson, Nev.) (17,18). Forty patients without clinical evidence of atherosclerotic vascular disease undergoing noncardiovascular procedures involving the abdomen or lower extremities were randomly selected to serve as controls for coagulation status. One-half of these control patients received general anesthesia, and one-half received general-epidural anesthesia and analgesia as described. Thromboelastography was performed on whole blood after induction of anesthesia and on the first postoperative day for the control patients and for the 80 vascular surgical patients.

Postoperatively, all patients were transferred to an intensive care unit (ICU) and received postoperative intensive care following standardized protocols. Postoperative hemodynamic variables, arterial blood gas tensions, electrolytes, hemoglobin, and urine output were monitored closely under the direction of a staff surgeon and an anesthesiologist who were not one of the authors and who were unaware of the goals of the study. Discharge of patients from the ICU was determined by the surgical staff and was dependent on the assessment of overall patient course and cardiopulmonary stability. Patients were transferred to a regular hospital bed only when they did not require vasoactive infusions, invasive monitoring, fluid administration above maintenance levels, or aggressive pulmonary therapy for at least 24 h.

Data Collection

The physicians and nurses involved in the care of the patients were unaware of the outcome variables that were being monitored. Data were collected by a full-time data manager. Preoperative patient demographics that might be associated with greater mortality and morbidity after vascular surgery (1–3) were selected for examination. Evidence of congestive heart failure (defined as classic chest radiographic changes in conjunction with either rales on lung auscultation or an S3 gallop on cardiac auscultation), history of angina, prior myocardial infarction, preoperative arrhythmias requiring treatment, and chronic hypertensive therapy were noted. Left ventricular dysfunction was defined by an ejection fraction of less than 0.4. Renal dysfunction (defined as a preoperative creatinine level greater than 1.4 mg/dL), diabetes mellitus, age, preoperative antianginal therapy (β-adrenergic or calcium channel blocking drugs and topical or oral nitrates), duration of operation, and estimated blood loss were also noted. Intraoperative hypertension was considered present if the systolic pressure exceeded 120% of the mean preoperative systolic blood pressure for more than 5 min; hypotension, if the systolic pressure was less than 80% of the mean preoperative systolic pressure for more than 5 min; and tachycardia, if the heart rate exceeded 120% of the mean preoperative rate or 100 beats/min for more than 5 min.

Postoperative observations of clinical outcome were made using prospectively defined definitions of morbidity (Table 1). Electrocardiographic ischemia was defined as $\geq$0.1 mV positive or negative horizontal ST segment shift, which extended at least 80 ms beyond the J point of the QRS complex in any lead. Hard copies of lead II or CS_5 were obtained every 4 h in the ICU and more frequently if changes suggestive of ischemia (ST segment or T wave abnormalities) or of arrhythmias appeared on continuous oscillographic displays. In addition, standard 12-lead electrocardiograms were recorded twice daily in the ICU. All hard-copy electrocardiographic recordings were calibrated using a 1-mV standard.

Postoperative vascular graft patency was determined by clinical examination and by Doppler measurements. Early vascular graft failure was defined as a return of preoperative clinical status, lack of significant improvement in Doppler measurements, or need of reoperation for thrombectomy or unplanned amputation of any portion of the affected limb. All patients in whom graft failure developed had intraoperative arteriograms performed at the completion of the initial procedure. These completion arteriograms were independently reviewed by two cardiovascular surgeons not involved in the primary operation; none of the patients with graft failure had any evidence of technical error such as intimal flap or anastomotic problems, and all had adequate outflow on completion of the operation. Deep venous thrombosis of the lower extremities was diagnosed by clinical examination and was documented with venography.

Data Analysis

Patient demographics, perioperative risk factors, and the incidence of postoperative morbidity were compared between the GEN and GEN-EPI group. Patient age, duration of operation, estimated blood loss,

Table 1. Definitions of Postoperative Morbidity

Complication	Definition
Major cardiovascular	
New myocardial infarction	Creatine phosphokinase or lactate dehydrogenase isoenzyme and electrocardiographic changes
Congestive heart failure	Classic radiographic changes with either rales, S3 gallop, or pulmonary artery occlusion pressure ≥18 mm Hg, if measured
Serious arrhythmias	Ventricular tachycardia, supraventricular tachyarrhythmias or heart block requiring treatment
Angina	Chest discomfort and electrocardiographic changes prompting pharmacologic therapy
Hypertensive crisis	Marked arterial blood pressure elevation with encephalopathy, myocardial ischemia, or congestive heart failure
Pulmonary	Tracheal intubation >24 h or tracheal reintubation and mechanical ventilation after initial extubation
Renal	Increase in serum creatinine ≥2 mg%
Neurologic	Sensory, motor, or reflex abnormalities anytime after surgery; global abnormalities within 2 days of operation
Gastrointestinal	Gastrointestinal hemorrhage with a decline in hemoglobin of 2 g%; acute surgical abdomen
Infectious	Pneumonia (radiographic infiltrate and two of three criteria: fever, leukocytosis, or positive sputum culture); localized infection with culture positive for a pathogen, requiring antibiotics and accompanied by either fever or leukocytosis

Table 2. Patient Characteristics

	GEN	GEN-EPI	P
No. of patients	40	40	
Age (yr)[a]	65.5 ± 9.9	69.6 ± 8.4	0.052
Sex (F) (%)	62.5	57.5	0.648
Previous vascular surgery (%)	30.0	32.5	0.809
History of transient ischemic attack or stroke (%)	15.0	17.5	0.762
History of chronic obstructive pulmonary disease (%)	20.0	20.0	1.00
History of angina (%)	35.0	50.0	0.175
Ejection fraction <0.4 (%)	15.0	22.5	0.390
Congestive heart failure (%)	2.5	10.0	0.166
Previous myocardial infarction (%)	25.0	47.5	0.036
History of hypertension (%)	72.5	62.5	0.339
Renal dysfunction (%)	17.5	30.0	0.189
Diabetes mellitus (%)	17.5	37.5	0.045
Antiarrhythmic medications (%)	27.5	32.5	0.626
β-Adrenergic blocker (%)	12.5	12.5	1.00
Calcium channel blocker (%)	35.0	30.0	0.633
Nitrates (%)	20.0	22.5	0.785
Infrainguinal revascularization (%)	50.0	62.5	0.260
Duration of operation (h)[a]	3.8 ± 1.3	3.5 ± 1.1	0.455
Estimated blood loss (mL)[a]	404 ± 242	462 ± 468	0.621

GEN, general anesthesia; GEN-EPI, combined general-epidural anesthesia.

[a] Values are mean ± SD.

duration of ICU and total postoperative hospital stay, and the total number of complications were compared between anesthesia groups using the Mann-Whitney U test. Thromboelastographic variables (R, K, α, and MA) were compared using analysis of variance with repeated measures. When appropriate, secondary tests were performed using the Tukey-a method. The conventional Pearson χ^2 statistic was used to compare all other data between groups (19). The null hypothesis was rejected when P was less than 0.05.

Patient characteristics from Table 2 were subjected to multivariate analysis using stepwise logistic regression to determine the best set of variables predictive of major cardiovascular complications (as defined previously). The variables in the predictor set were found by a forward selection process such that the P value associated with the introduction of additional variables was greater than 0.05. The estimate of the coefficient in the regression equation and the estimate of the odds ratio calculated from this coefficient were maximum likelihood estimates. The odds ratio is the relative odds of the occurrence of a major cardiovascular complication associated with a change in the predictor variable.

Results

The comparison of group characteristics that might influence outcome after major peripheral vascular operation is presented in Table 2. The study groups are similar in terms of preoperative characteristics, chronic drug therapy, and surgical variables, except for a greater incidence of diabetes mellitus and prior myocardial infarction in the GEN-EPI group. Intraoperatively, the incidence of hypertension (30.0% vs 25.0%) and tachycardia (12.5% vs 7.5%) did not differ significantly between the GEN and GEN-EPI groups, respectively.

There were no baseline differences in coagulation state between the vascular surgery patients in the GEN or GEN-EPI groups (Table 3). After induction of anesthesia (baseline), patients with atherosclerotic vascular disease had accelerated coagulability (repre-

Table 3. Effect of Anesthesia on Thromboelastographic Coagulation Variables

Variables	Baseline Vascular	Baseline Nonvascular	Postoperative Vascular	Postoperative Nonvascular
General anesthesia (*n*)	40	20	40	20
R (min)	11.2 ± 2.3	12.6 ± 2.2	11.1 ± 2.1	12.6 ± 1.5
K (min)	4.8 ± 0.9	5.5 ± 1.3	4.5 ± 0.9	5.1 ± 0.8
α (deg)	56.8 ± 4.3[a,b]	48.7 ± 7.8[b]	59.0 ± 6.4[a,c,d]	49.6 ± 8.2[d,e]
MA (mm)	61.8 ± 4.5[f,g]	50.2 ± 6.8[g]	63.9 ± 5.3[f,h,i]	51.8 ± 6.9[i,j]
Combined general-epidural anesthesia (*n*)	40	20	40	20
R (min)	11.4 ± 1.7	12.2 ± 2.3	11.5 ± 1.5	12.6 ± 1.5
K (min)	4.8 ± 0.7	5.2 ± 1.2	4.9 ± 0.8	5.4 ± 0.7
α (deg)	56.2 ± 6.0[k,l]	48.0 ± 5.1[l,m]	48.1 ± 5.1[c,k,n]	45.8 ± 3.9[e,m,n]
MA (mm)	62.0 ± 4.2[o,p]	51.7 ± 4.6[p,q]	53.8 ± 5.2[h,o,r]	47.8 ± 4.1[j,q,r]

Values are mean ± SD.
[a–r]Designate significantly different pairs, $P = 0.05$.

sented by larger α and MA values) compared with control patients without clinical evidence of atherosclerotic vascular disease (Table 3). These thromboelastographic markers of fibrinogen-platelet activity increased on the first postoperative day in vascular surgery patients receiving general anesthesia. Conversely, use of GEN-EPI anesthesia in patients undergoing vascular surgery was associated with a significant decline in postoperative α and MA values (Table 3). A decline of smaller magnitude in postoperative α and MA values from baseline was seen in control patients receiving GEN-EPI anesthesia for nonvascular surgery. Postoperatively, vascular surgery patients in the GEN-EPI group had values of α and MA that approached but still exceeded those of nonvascular surgery patients who received similar anesthetic management.

The average duration of epidural catheter use for analgesia was 2.40 ± 0.98 postoperative days. The average pain scores in the GEN-EPI group on the first three postoperative days were 2.3 ± 2.6, 1.1 ± 1.4, and 0.8 ± 1.0, respectively, as measured on a visual analogue scale from 0 to 10 in which a score of 0 represents no pain and a score of 10 represents intense pain.

The duration of hospital stay after surgical procedures performed under GEN-EPI anesthesia was 10.7 ± 6.8 days compared with 13.2 ± 11.7 days in those receiving general anesthesia alone ($P = 0.565$). The duration of ICU stay was longer in the GEN group compared with the GEN-EPI group (3.3 ± 6.9 vs 1.5 ± 1.4 days; $P = 0.031$). This longer ICU stay after operation was associated with a larger number of serious complications in patients receiving general anesthesia alone (Table 4). In the GEN group, one or more postoperative complications developed in 18 of 40 patients compared with 8 of 40 in the GEN-EPI group. The number of patients experiencing two or more complications was also larger in the GEN group (11/40 vs 3/40). There was no in-hospital mortality in either group. An analysis of complication types showed a larger incidence of cardiovascular and infectious complications and a larger incidence of peripheral vascular occlusions (arterial graft failure or deep venous thrombosis) in the GEN group (Table 4). The larger incidence of vascular graft failure in the

Table 4. Postoperative Morbidity and Mortality

	GEN (*n* = 40)	GEN-EPI (*n* = 40)	*P*
Mortality	0	0	
Morbidity			
Cardiovascular[a]	11	4	0.045
Myocardial infarction	3	0	0.077
Congestive heart failure	4	2	0.409
Ventricular tachyarrhythmia	4	0	0.040
Supraventricular tachyarrhythmia	7	3	0.176
Hypertensive crisis	1	0	0.314
Angina	1	1	1.00
Heart block	2	0	0.152
Respiratory[a]	5	1	0.089
Prolonged endotracheal intubation	5	1	0.089
Reintubation	1	0	0.314
Renal insufficiency	3	1	0.305
Neurologic complications	3	0	0.078
Gastrointestinal	1	2	0.556
Infectious[a]	8	2	0.043
Pulmonary	4	0	0.040
Urinary tract	4	2	0.409
Vascular occlusions[a]	9	1	0.007
Vascular graft failure	8	1	0.013
Deep venous thrombosis	1	0	0.314
Total complications	52	13	0.011
Number of patients with			
≥1 Complications	18	8	0.017
≥2 Complications	11	3	0.019

GEN, general anesthesia; GEN-EPI, combined general-epidural anesthesia.
[a]Number of patients with one or more complications within category.

Table 5. Thromboelastographic Coagulation Data for Patients With Vascular Graft, Coronary Artery, or Deep Vein Thromboses

	Baseline		Postoperative	
Variables	Thrombosis ($n = 12$)	No thrombosis ($n = 68$)	Thrombosis ($n = 12$)	No thrombosis ($n = 68$)
R (min)	10.9 ± 2.6	11.3 ± 1.9	10.7 ± 2.7	11.4 ± 1.6
K (min)	4.5 ± 0.9	4.8 ± 0.8	4.5 ± 1.1	4.7 ± 0.8
α (deg)	57.2 ± 6.0	56.4 ± 5.0^{a}	59.1 ± 9.5^{b}	52.6 ± 7.3^{a,b}
MA (mm)	61.2 ± 4.6	61.9 ± 4.3^{c}	63.7 ± 7.9^{d}	58.0 ± 6.8^{c,d}

Values are mean ± SD.
$^{a-d}$Designate significantly different pairs, $P = 0.05$.

GEN group was also associated with a larger incidence of reoperation on the affected limb (7/40 vs 1/40, $P = 0.025$). The incidence of postoperative electrocardiographic evidence of ischemia did not differ between the GEN and GEN-EPI groups (15/40 vs 13/40, respectively; $P = 0.639$). In addition to the larger overall incidence of postoperative infections, there was a larger incidence of pulmonary infections in the GEN group (4/40 vs 0/40). Five of the 40 patients in the GEN group required tracheal intubation and mechanical ventilation for longer than 24 h postoperatively, and one of these patients required tracheal reintubation and mechanical ventilation. None of the patients in the GEN-EPI group required tracheal reintubation, and only one of 40 patients in the GEN-EPI group required mechanical ventilation for more than 24 h.

Postoperatively, three patients in the GEN group experienced neurologic complications: one patient suffered a hemispheric cerebral infarct, another had severe exacerbation of multiinfarct dementia requiring prolonged rehabilitation, and one had mental obtundation and symptoms consistent with a transient ischemic event that resolved without sequelae. None of the patients receiving GEN-EPI anesthesia experienced postoperative neurologic complications. Significant gastrointestinal complications developed in three patients after operation: one patient required reoperation for removal of a portion of ischemic small bowel and gangrenous cholecystitis; ischemic colitis with lower gastrointestinal bleeding developed in one, requiring a diverting colostomy; and one experienced a severe form of Olgilvie's syndrome postoperatively. There was no difference in the occurrence of these events between anesthesia groups, nor were there differences in any outcome variable between type of surgical procedure.

To determine if the occurrence of thrombotic events in the postoperative period was associated with hypercoagulability as measured by thromboelastography, coagulation data for patients with clinical evidence of coronary artery, deep vein, or vascular graft thrombosis (12 patients experiencing 13 events) were compared with that for patients without these complications (Table 5). There were no baseline differences in coagulation state detectable by thromboelastography between patients with or without postoperative thrombotic complications. However, accelerated coagulation was observed postoperatively in those patients experiencing thrombotic events compared with those without thrombotic events ($n = 68$). Of those patients in whom postoperative thrombosis of a coronary artery, deep vein, or vascular graft developed, 11 received general anesthesia alone and one received GEN-EPI anesthesia ($P = 0.002$). Multivariate analysis using stepwise logistic regression considered all of the perioperative factors listed in Table 2 as well as the type of anesthesia. The presence of preoperative congestive heart failure (β coefficient $= 3.02$, $P = 0.009$) and the use of general anesthesia without epidural analgesia (β coefficient $= 1.85$, $P = 0.022$) were significant predictors of postoperative cardiovascular complications with odds ratios of 20.51 and 6.36, respectively (Table 6). None of the other perioperative variables had predictive value.

Discussion

The choice of anesthesia for patients undergoing major peripheral vascular surgery remains controversial. Yeager et al. (4) included patients undergoing major peripheral vascular surgery as a subset of high-risk surgical patients exhibiting a significantly larger cardiovascular complication rate after general anesthesia compared with combined regional-general anesthesia. Another randomized trial (20) and a retrospective review (5) were not able to demonstrate differences in mortality or cardiac morbidity in patients receiving central neuraxial anesthesia compared with general anesthesia for peripheral vascular surgery. These conflicting results may be attributed to differences in population characteristics, intraoperative management, and, perhaps most importantly,

Table 6. Multivariate Predictors of Cardiovascular Complications

	P	β	Odds ratio
Variables in the equation			
Congestive heart failure	0.009	3.02	20.51
General anesthesia without epidural analgesia	0.022	1.85	6.36
Variables not in the equation			
Diabetes	0.188		
History of angina	0.255		
History of chronic obstructive pulmonary disease	0.269		
Age ≥70 yr	0.377		
Previous myocardial infarction	0.400		
Renal dysfunction	0.496		
Estimated blood loss	0.630		
Previous vascular surgery	0.680		
Ejection fraction <0.4	0.689		
Duration of surgery	0.719		
History of hypertension	0.943		
Infrainguinal revascularization	0.966		

postoperative care (4,5,20). Specifically, postoperative complications that occur many hours or days after operation may be highly influenced by postoperative care, including the provision of better analgesia. The manner and extent of this influence on postoperative morbidity that occurs temporarily separated from intraoperative events remains speculative but may involve stress-modulated or direct anesthetic effects on the coagulation system.

In our study, patients about to undergo peripheral vascular surgical procedures were hypercoagulable before operation compared with control patients without atherosclerotic vascular disease; the use of epidural anesthesia and analgesia attenuated this hypercoagulability postoperatively. Although we did not measure biochemical markers of the stress response, decreases in cortisol, renin, aldosterone, and catecholamine levels have been associated with epidural anesthesia and analgesia, especially when used for procedures involving the abdomen and lower extremities (4,11–13,16,21–23). Stress-mediated increases in angiotensin (secondary to higher renin activity) and in catecholamines can increase platelet aggregation (24,25). Reduction of the stress response with epidural anesthesia and analgesia may indirectly affect platelet function (16) and may be particularly important in patients with atherosclerotic disease who have a primary tendency to have accelerated platelet activity. Epidural anesthesia and analgesia may affect the coagulation state postoperatively by attenuating the usual catabolism of proteins seen in patients undergoing vascular reconstruction (8). The metabolic response to stress is manifested by accelerated protein breakdown, increased hepatic synthesis of selected proteins (acute-phase reactants including fibrinogen) (26), and decreased synthesis of other proteins (such as antithrombin III) (8). Improved fibrinolytic activity with a larger concentration of postoperative plasminogen activator occurs after extradural anesthesia and analgesia, compared with general anesthesia with parenteral analgesics for postoperative pain (14). The association of epidural anesthesia and analgesia with reduced postoperative stress responses (27–29) may translate to higher antithrombin III and lower fibrinogen levels with attenuated platelet activity postoperatively, consistent with the thromboelastographic findings in this study. The effects of epidural anesthesia and analgesia on coagulation are complex, and elucidation of the exact mechanisms by which epidural anesthesia and analgesia attenuate accelerated postoperative coagulability in patients undergoing vascular reconstruction will require further study.

The influence of epidural anesthesia and analgesia on coagulation may have important clinical consequences. Our data support the hypothesis that accelerated coagulability may be associated with thrombotic events in coronary arteries and in peripheral vascular grafts. Although the utility of thromboelastography as a coagulation test remains controversial, primarily because of its relatively nonspecific characterization of the hemostatic process, this study supports the use of thromboelastography as a useful biologic marker for accelerated coagulability in this high-risk population. As used in this study, thromboelastography does not allow differentiation of the exact coagulation mechanisms that are altered after major vascular surgery. The data do suggest that monitoring the coagulation state, especially platelet activity, may identify patients who would benefit from postoperative therapy such as antiplatelet drugs or other forms of anticoagulation.

Effects on coagulation probably reflect only one possible mechanism by which epidural anesthesia and analgesia may modulate outcome in high-risk patients undergoing vascular surgery. Blood flow in the legs of patients with occlusive atherosclerotic disease is increased after epidural anesthesia (30). This effect may be enhanced when postoperative epidural analgesia includes a dilute solution of local anesthetic to maintain some degree of sympathetic block after arterial reconstruction and may have contributed to improved short-term graft patency in those patients receiving epidural analgesia in this study.

In addition to the effects on coagulation and vascular graft patency, a lower total number of complications, shorter duration of ICU stay, fewer infections, and a trend toward fewer respiratory complications (manifested as a lower incidence of prolonged tracheal intubation and respiratory infections) were observed in the patients who received epidural anesthesia and analgesia. Previous findings of shorter duration of ventilatory support and ICU stay in patients receiving postoperative epidural analgesia have been questioned because of the inclusion of high-dose opioid anesthesia in the nonepidural group (4). A strength of the current study is the confirmation of these findings in the absence of this potentially confounding factor. Despite the use of general anesthesia techniques with differing effects on the neuroendocrine response to surgical stress, these data and those of Yeager et al. (4) both demonstrate that epidural anesthesia and analgesia is associated with a beneficial effect on postoperative morbidity. These findings suggest that any potential benefits of epidural anesthesia and analgesia may be related more to postoperative rather than intraoperative influences. Several mechanisms may explain the latter effects of epidural anesthesia and analgesia: better analgesia, decreased duration of endotracheal intubation and mechanical ventilation which diminish pulmonary defense mechanisms against infection, longer duration of postoperative ICU stay which is associated with a higher risk of nosocomial infections, and better maintenance of postoperative immunocompetence (31). Our study design does not allow us to confirm or refute these hypotheses but does reconfirm the beneficial effects of a combination of general with epidural anesthesia and analgesia compared with general anesthesia with routine postoperative pain management on several aspects of outcome (4).

The major goal of this study was to compare the use of combined general-epidural anesthesia and continuous epidural analgesia with a specific general anesthetic technique followed by the on-demand, intermittent administration of opioids for postoperative analgesia. No attempt was made to provide equal degrees of postoperative analgesia in the study groups, but rather, these modalities were compared as to how they would commonly be used in clinical practice. As a consequence, to avoid confounding influences on the administration of and response to intermittent, on-demand analgesia as it is usually administered, these patients were not visited by a member of the acute pain service. In contrast, an essential standard of postoperative epidural analgesia is the involvement of an acute analgesia service that frequently evaluates patients to assess the efficacy of analgesia, to ensure the use of supplemental analgesic medications, and to evaluate and treat side effects such as pruritus and nausea. The excellent pain scores in the epidural analgesia group attest to the efficacy of the epidural analgesia service in these high-risk patients. Although pain scores were intentionally not obtained in the GEN group to avoid altering the intrinsic nature of intermittent, on-demand pain control and other aspects of these patients' care, it is very likely that the analgesia was less than that observed in the epidural group. The current study design does not allow confirmation or rebuttal of the hypothesis that improved outcome in the setting described may have been related primarily to different degrees of postoperative analgesia. Rather, it confirms earlier findings that epidural anesthesia and analgesia, used in the manner described, is associated with better outcomes compared with on-demand, intermittent opioid analgesia. Although plausible, it seems unlikely that visitation by acute pain service personnel of those patients not receiving epidural analgesia after major vascular surgery could result in similar improvements in outcome, as analgesia would still remain intermittent. Further studies will be required to clarify whether other forms of analgesic therapy, such as patient-controlled analgesia with or without continuous opioid infusions, will also be associated with similar outcome differences. Defining the relative contribution of effective analgesia per se, neuraxial sympatholysis, improvements in lower extremity blood flow, and reduction in hypercoagulability to clinical outcomes will also require further studies to determine the precise mechanism(s) by which epidural anesthesia and analgesia may be related to these findings. Because our study was designed as an observational critique of the clinical outcome of two methods of perioperative anesthetic management, interpretation of the findings is limited in that specific mechanisms were not sought to explain the intergroup differences.

Although previous data have suggested an effect of epidural anesthesia and analgesia on postoperative mortality in high-risk patients (4), we are not able to confirm or refute these findings as no in-hospital mortality was observed in this study. Differences in surgical populations, sample sizes, and patient management may be responsible for differences in the incidence of mortality in different studies. Our data do, however, confirm that preoperative congestive heart failure is a significant predictor of adverse cardiovascular outcome in high-risk patients undergoing noncardiac surgery (3).

Despite the levels of significance of our major findings, an important limitation of this investigation is the small number of patients assigned to each anesthetic group. Although univariate and multivariate statistical analysis failed to detect any significant bias against those patients assigned to the GEN group, there may have been unquantifiable differences between the randomized anesthesia groups. In addition, a very select patient population was examined, so that the results of this study may not be generalizable to patient subsets undergoing different surgical procedures.

In summary, we have demonstrated that patients with atherosclerotic occlusive vascular disease are hypercoagulable relative to control patients, and that the use of epidural anesthesia and analgesia attenuates this hypercoagulability after lower extremity revascularization. The use of general anesthesia combined with epidural analgesia using dilute solutions of local anesthetic and narcotic is associated with improved outcome compared with general anesthesia and routine, on-demand narcotic analgesia for major peripheral vascular surgery.

The authors thank Elizabeth R. Corey, RN, and Sharon Grande, RN, for their assistance in data collection.

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Transesophageal Doppler Cardiac Output Monitoring: Performance During Aortic Reconstructive Surgery

Albert C. Perrino, Jr., MD, Julia Fleming, MB, BS, FFARACS, and Kenneth R. LaMantia, MD

Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut

Transesophageal Doppler (TED) monitoring provides continuous, noninvasive monitoring of cardiac output by measurement of aortic flow velocities. Because of the effects on aortic flow dynamics resulting from atherosclerosis, aortic cross-clamping, and wide variations in arterial blood pressure, the validity of TED monitoring during aortic surgery is unresolved. The authors prospectively evaluated a second-generation TED cardiac output monitor in 42 patients undergoing aortic reconstructive surgery. Four hundred eighty-nine simultaneous measurements of TED and thermodilution cardiac output were obtained. Transesophageal Doppler measurements were highly correlated to thermodilution measurements (R = 0.94); however, Bland-Altman analysis revealed a moderate error in the TED measurements (2 SD of the bias = 1.4 L/min). Trending analysis showed that TED monitoring accurately tracked changes in thermodilution cardiac output. Placement of an aortic cross-clamp resulted in significant reductions in the accuracy of Doppler measurements. Arterial blood pressure variations did not systematically affect the accuracy of the transesophageal technique. Limitations of TED monitoring, including a difficult calibration procedure, poor performance during aortic cross-clamping, and the need for probe repositioning, suggest further development is warranted.

(Anesth Analg 1991;73:705–10)

Transesophageal Doppler (TED) monitoring provides continuous, noninvasive monitoring of cardiac output (CO) by measurement of aortic flow velocities. The initial TED monitors developed for clinical use performed inconsistently in anesthetized patients and thus failed to gain wide clinical acceptance (1–4). Recent engineering advances have produced a second-generation TED CO monitor, Accucom 2 (Datascope Corp.), which has significantly improved performance compared with the earlier models (5,6). However, the validity of TED measurements in specific clinical settings has not been established.

Cardiac output monitoring is commonly used for patients undergoing aortic surgery. The validity of TED measurements in these patients remains unclear because of several factors. Accurate Doppler measurements of aortic flow assume a circular aorta and laminar flow with a blunt velocity profile (7). Severe atherosclerotic disease resulting in occlusive and aneurysmal disease as well as a tortuosity of the aorta may invalidate these assumptions of aortic flow essential to accurate Doppler measurements. Surgical manipulation of the aorta and placement of an aortic cross-clamp are also potential sources of error in Doppler monitoring (1,2). Additionally, large changes in arterial blood pressure, common during aortic reconstructive surgery, may reduce the accuracy of TED measurements (2,8–10). The influence of these factors on Doppler monitoring has not been systematically examined.

This investigation is a prospective evaluation of TED CO monitoring during aortic surgery. We examined the effects of vascular disease, aortic cross-clamping, and arterial blood pressure variation on the accuracy of TED monitoring by comparing Doppler to thermodilution CO measurements.

Methods

Consecutive patients scheduled for abdominal aortic reconstructive surgery were screened for the study following an ethical committee approved protocol. Patients with a history or examination findings consistent with intracardiac shunt or aortic or tricuspid valve disease were excluded. Anesthetic management, including monitoring and technique, was at the discretion of the clinical anesthesiologist. Both inhalational and narcotic-based techniques were used.

The TED device requires a three-step procedure for

Accepted for publication August 16, 1991.

Address correspondence to Dr. Perrino, Yale University School of Medicine, Department of Anesthesiology, 333 Cedar Street, New Haven, CT 06510.

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0003-2999/91/$3.50

CO determination. First, aortic cross-sectional area is calculated by nomogram based on patient characteristics, including age, sex, height, and weight. Second, after tracheal intubation, a 20F esophageal stethoscope with a piezoelectric crystal mounted at its tip is inserted and positioned to optimize Doppler signals. Third, the esophageal Doppler signals are calibrated with ascending aortic flow signals obtained with a transcutaneous Doppler probe placed externally at the suprasternal notch. The calibration is based on a proportionality constant (K-factor), which equals the ratio of ascending aortic to descending aortic blood velocity. The K-factor was determined in each patient at the initial calibration and was not changed during the procedure.

To optimally position the Doppler probes, the TED provides a real-time display of the blood velocity profile and a digital measure of received Doppler signal strength. Once calibrated, the TED signals permit continuous measurement of CO based on descending aortic flow signals. These values represent the average measurement over a 15-s interval.

Doppler examinations were performed by an ultrasonography team consisting of two of the authors (A.P. and J.F.) who had previous clinical experience with Doppler velocitometry and who were blinded to the thermodilution CO determinations. The esophageal probe was adjusted during the surgical procedure when the quality of the Doppler signal deteriorated. The basis for guiding proper probe position was the audible Doppler frequency shift and the real-time displays of the aortic velocity profile and the Doppler signal quality. The initial positioning and any subsequent repositioning of the esophageal probe was based solely on the information provided by the TED computer without knowledge of the thermodilution CO.

As a reference standard, thermodilution CO measurements were obtained by the patient's anesthesiologist at end-expiration using room temperature injectate and a dedicated, calibrated computer (COM-1, American Edwards). The anesthesiologist was blinded to the TED CO determinations. During a 5-min period where the mean arterial pressure variation was less than ±5 mm Hg, repeated simultaneous thermodilution CO and TED CO measurements were obtained and defined an epoch. An epoch was accepted for analysis when three CO values with less than a 15% variation, largest to smallest, were obtained for each method of CO determination.

Data were divided into three groups for analysis: (a) preclamp (before aortic cross-clamping), (b) clamp (the period when an aortic cross-clamp was in position), and (c) postclamp (after removal of an aortic cross-clamp). Comparison of simultaneous Doppler CO and thermodilution CO measurements included calculation of the mean Doppler CO and mean thermodilution CO for each epoch. The mean CO values for each epoch were then analyzed by simple linear regression with calculation of the slope, intercept, and standard error of the estimate. Pearson's product-moment correlation coefficient was also determined.

The technique of Bland and Altman was used to define the agreement between simultaneous TED and thermodilution measurements (11). The difference between simultaneous TED and thermodilution measurements provides a measure of bias. The mean bias represents the systematic error between the two measurement techniques. The standard deviation of the bias is a measure of the accuracy of Doppler measurements. Mean absolute percent error represents the error in the Doppler technique as a percentage of actual CO. With the Bland-Altman method, the actual CO for an epoch is defined as the mean of the Doppler and thermodilution measurements.

To evaluate the ability of TED monitoring to detect changes in thermodilution CO during the procedure (e.g., trending capability), we calculated the percent change of CO between successive epochs for each measurement technique. Regression and descriptive analysis was then performed to compare the percentage change in thermodilution CO with the percentage change in Doppler CO.

To determine the effect of intraoperative arterial blood pressure changes on Doppler measurements, regression analysis was performed comparing the difference between Doppler CO and thermodilution CO to the percent change in blood pressure. The percent change in blood pressure was normalized to the initial arterial blood pressure measured during calibration of the esophageal probe. That is, for an epoch at time t:

$$\text{Percent change in MAP}_t = (\text{MAP}_t - \text{MAP}_{t0}/\text{MAP}_{t0}) \times 100,$$

where MAP_t is the mean arterial pressure at time t and MAP_{t0} is the MAP during calibration of the esophageal probe. Mean arterial pressure was determined using a radial artery catheter and a calibrated pressure transducer.

Student's *t*-test and F-test were used to determine if statistically significant differences in the performance of the TED occurred with aortic manipulation. In both tests a *P* value of less than 0.05 was considered to be statistically significant.

Results

Forty-two patients were studied including three patients who were excluded because of poor Doppler

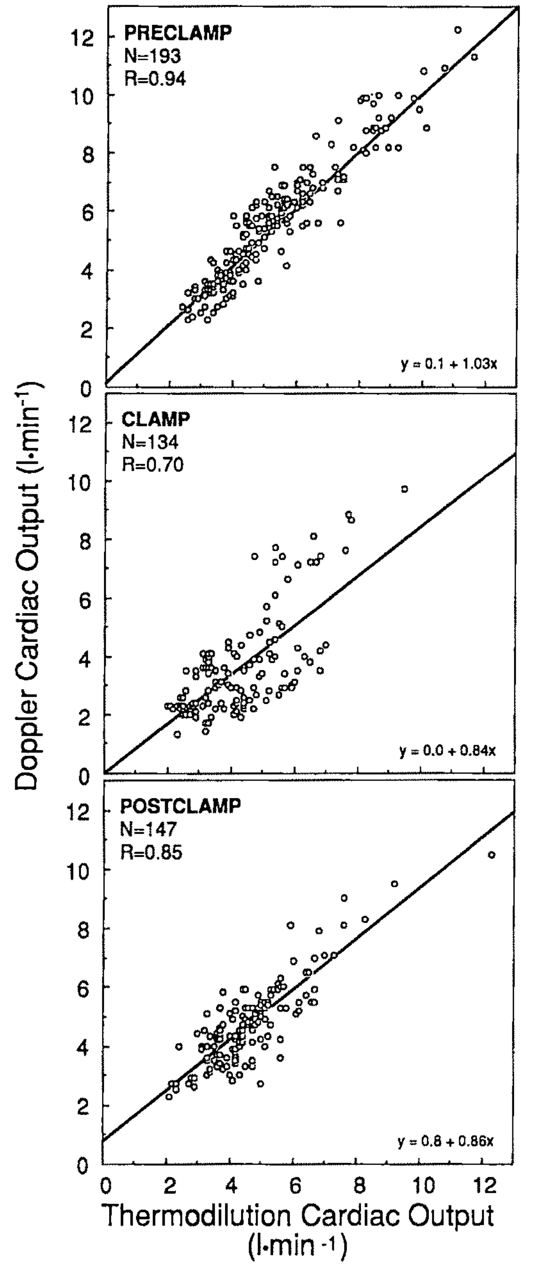

Figure 1. Scattergrams of simultaneous transesophageal Doppler and thermodilution cardiac output measurements. Excellent correlation is seen in the preclamp and postclamp groups.

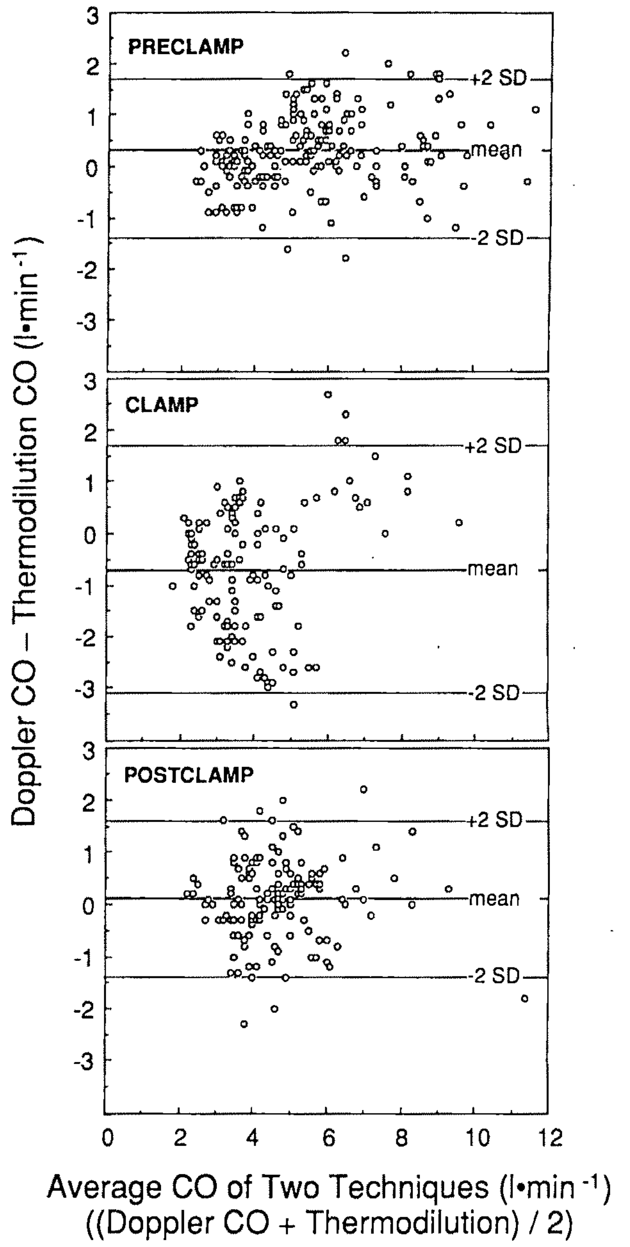

Figure 2. The difference between simultaneous Doppler and thermodilution cardiac output (CO) measurements is plotted against the average CO. Agreement between transesophageal Doppler and thermodilution measurements is significantly greater in the preclamp and postclamp groups.

signal quality. Cardiac output determinations were divided into 489 epochs for analysis.

The scattergrams and regression analyses of the data are shown in Figure 1. Before aortic cross-clamping there was a strong correlation between Doppler CO and thermodilution CO ($R = 0.94$). After placement of an aortic cross-clamp, the correlation between measurements decreased ($R = 0.72$), but improved after removal of the aortic clamp ($R = 0.88$).

Figure 2 is a plot of the difference between simultaneous thermodilution and Doppler measurements. The mean bias and two standard deviation range of the bias are also plotted. The agreement is best in the preclamp period where the two standard deviation range is 1.4 L/min. After placement of the aortic cross-clamp, the accuracy of the Doppler technique decreased with a two standard deviation range of 2.6 L/min. Once the aortic clamp was released, the agreement between Doppler and thermodilution improved with the two standard deviation range decreasing to 1.5 L/min. There was no significant dif-

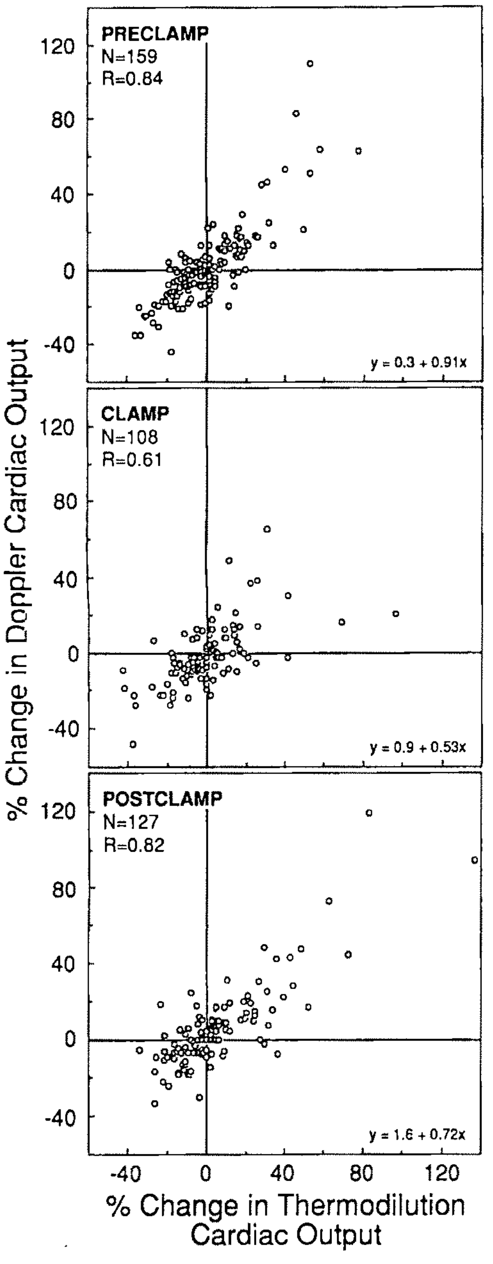

Figure 3. The trending capability of transesophageal Doppler is illustrated by the four-quadrant scattergram of percent change of TED and percent change of thermodilution cardiac output measurements. Transesophageal Doppler reliably tracks both increases and decreases of cardiac output.

ference in accuracy of the Doppler technique between the preclamp and postclamp periods. However, error increased significantly during the clamp period ($P < 0.05$).

The trending capability of TED is illustrated in Figure 3. There is a strong correlation between the percent change in thermodilution CO and the percent change in Doppler CO in the preclamp and postclamp periods. Furthermore, TED accurately trended during large changes in thermodilution CO. Transesophageal Doppler trended correctly 89 of the 100 times (89%) thermodilution CO changed more than ±15%. During the clamp phase the correlation decreased ($R = 0.72$) and the Doppler trended accurately 26 of the 33 times (79%) thermodilution CO changed more than ±15%.

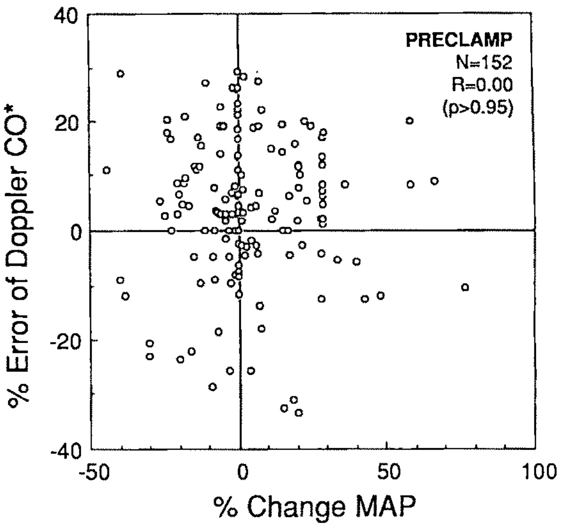

Figure 4. Regression analysis reveals no correlation between error of the Doppler cardiac output (CO) measurements and changes in mean arterial pressure (MAP). *Percent error of Doppler CO is defined as ((Doppler CO − thermodilution CO)/(Doppler CO + thermodilution CO)) × 200.

Regression analysis revealed no significant correlation between arterial blood pressure changes and accuracy of the Doppler technique (Figure 4).

Discussion

Transesophageal Doppler offers a noninvasive alternative to thermodilution for CO monitoring. After an initial calibration procedure, TED provides continuous CO monitoring based on descending aortic blood flow. Although advances in design have improved the performance of TED monitoring, the validity of TED measurements during aortic surgery has not been established.

This study evaluates TED monitoring in patients with severe atherosclerotic disease undergoing aortic surgery. Atherosclerosis, with resulting intimal hyperplasia and occlusive and aneurysmal disease, can significantly alter the flow dynamics and geometry of the aorta. This could result in inaccurate estimations of CO by the Doppler method (7). Placement of an aortic cross-clamp during construction of the aortic graft may also introduce error in Doppler measurements (1).

The K-factor, which converts descending aortic signals to ascending aortic flow velocities, is cited as another potential source of error with the transesophageal approach (1,2,8–10). The K-factor is calculated during the initial calibration procedure and is not adjusted during the course of surgery. Changes in arterial blood pressure, surgical stress, and aortic manipulation, as seen during aortic and open heart surgery, are clinical factors that may alter the K-factor. Significant fluctuations of the K-factor during surgery would produce errors in Doppler CO measurements.

To examine the effects of these factors on the performance of Doppler CO monitoring, the present investigation evaluated TED monitoring in patients undergoing aortic reconstructive surgery. Before aortic cross-clamping, Doppler and thermodilution measurements were highly correlated and Doppler accurately tracked changes in thermodilution CO. Bland-Altman analysis, however, does reveal a moderate error in the Doppler technique. As a ± two standard deviation range will delineate the 95% limit of agreement, any given Doppler measurement can be in error by ±1.4 L/min from a matched thermodilution value. The trending data do reveal that Doppler accurately tracks changes in CO.

The agreement between Doppler and thermodilution seen before aortic cross-clamping can be partly attributed to study design. The within-technique variability of thermodilution is widely recognized and has led some authors to question the appropriateness of thermodilution as a reference standard (12–14). In the clinical setting, changes in thermodilution CO of 15%–20% are required to reliably conclude that a real change in CO has occurred (15). To minimize the effects of thermodilution CO variability on evaluation of Doppler accuracy, data during any epoch were accepted only when at least three thermodilution measurements varied by less than 15%. Although reproducibility does not ensure accuracy of the thermodilution technique, it is a prerequisite. In contrast, the within-technique variability of Doppler CO measurements is extremely low (16). This is in part due to computer averaging of the Doppler signals over 15 beats.

The real-time display of flow signals also aids in limiting the error of Doppler measurements. The continuous display of the Doppler velocity profile and signal quality enabled the operator to detect decay of the esophageal signal and to adjust the probe position. The frequency of probe repositioning varied from one to five times a case. As the Doppler operator continually monitored the Doppler device in this investigation, it remains to be demonstrated whether a clinician will be as prompt and reliable in diagnosing a suboptimal Doppler signal.

Our data show that in the clinical setting, changes in arterial blood pressure do not affect the accuracy of Doppler monitoring in these patients. Atherosclerosis and the aging process cause significant changes in the pulsatile characteristics of the arterial system, resulting in a significant decrease of arterial distensibility in this patient population (17–19). Several studies utilizing pulse wave velocity recordings demonstrate a twofold to threefold decrease in arterial compliance in elderly patients with atherosclerosis (19–22). We propose that the more rigid vasculature dampens the fluctuations in descending aortic diameter caused by blood pressure changes and thus reduces the variability of the K-factor and limits the error of Doppler measurements. Investigations utilizing both Doppler and two-dimensional imaging of aortic dimensions to specifically examine the effects of atherosclerosis on aortic flow dynamics are required to confirm this hypothesis.

Aortic manipulation reduces the accuracy of TED monitoring. Placement of an aortic cross-clamp below the level of the renal arteries markedly increased the mean bias, standard deviation of the bias, and mean percent error of Doppler measurements. The esophageal probe monitors descending aortic flow at the midthoracic level, well above the origin of the renal arteries. The increased error seen with placement of an aortic cross-clamp may reflect alteration in the relationship between ascending and descending aortic flows or a disturbance of the descending aortic flow profile. For example, increased turbulence with aortic clamping would disrupt the laminar flow profile essential to Doppler measurements. A pulse wave Doppler examination of the aortic flow profile would aid in defining the aortic flow dynamics during aortic cross-clamping.

A frequent difficulty in this patient group was obtaining suprasternal Doppler measurements. Tortuosity of the ascending aorta, obesity, and emphysematous changes of the thorax complicate transcutaneous suprasternal probe measurements of ascending aortic flow. We were able to obtain adequate suprasternal Doppler signals in several patients who would not likely have tolerated the procedure awake. We were unable to obtain adequate Doppler signals in three patients. In another three patients interrogation of the innominate artery was identified by an atypical velocity profile (prolonged flow time and sharp upstroke) and adjustment of the suprasternal probe was made to interrogate the proper vessel. We believe the operator skill required and the frequent difficulty encountered with suprasternal Doppler measurements are drawbacks to the clinical acceptance of the TED technique.

In conclusion, we have demonstrated the accuracy of TED CO monitoring in patients with severe aortoiliac disease. Although the effects of atherosclerosis on Doppler monitoring are varied, they do not restrict the use of the TED. Limitations of the TED approach, including a difficult calibration process, the need for probe repositioning, and its poor performance during aortic cross-clamping, suggest that further development is warranted.

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Halothane Does Have Protective Properties in the Isolated Ischemic Rat Heart

André Coetzee, FFA(SA), FFARCS, MD, PhD, Wim Brits, BSc, Sonia Genade, BSc,
and Amanda Lochner, PhD, DSc

Department of Anesthesiology and Medical Research Council Unit for Molecular and Cellular Cardiology, University of Stellenbosch Medical School, Tygerberg, South Africa

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To determine whether halothane has protective effects on the ischemic heart, the influence of various concentrations (0.5%–1.5%) of halothane on metabolic and functional recovery during reperfusion after 60-min hypothermic (20°C) and 40-min normothermic cardioplegic arrest was determined in the isolated rat heart. Halothane was administered either before and after arrest or intermittently during arrest. Hearts not receiving halothane demonstrated a reduction in adenosine triphosphate (ATP) content from a control value of 20.35 ± 1.66 μmol/g dry wt (mean ± SEM) (before arrest) to 9.34 ± 1.12 μmol/g dry wt at the end of arrest ($P < 0.001$). The myocardial ATP content, when measured 20 min after arrest and during reperfusion, remained decreased (9.57 ± 0.62 μmol/g dry wt). Under these experimental conditions, aortic flow was reduced from 43.62 ± 2.40 mL/min before arrest to 1.80 ± 1.80 mL/min 20 min after arrest and during reperfusion ($P < 0.001$). The administration of adrenaline after 20 min of reperfusion resulted in partial recovery to 22.01 ± 8.36 mL/min. Administration of halothane (0.5%) before the cardioplegic period was associated with a reduction of ATP at the end of the normothermic arrest (4.02 ± 0.38 μmol/g dry wt; $P < 0.01$), but the ATP increased significantly (13.45 ± 0.32 μmol/g dry wt) when measured after the arrest and after 20 min of reperfusion and stimulation with adrenaline. The administration of halothane during the control period (before arrest) reduced aortic flow from 43.24 ± 1.11 to 28.70 ± 1.84 mL/min, whereas it averaged 6.08 ± 2.03 ($P < 0.001$) and 39.65 ± 3.49 mL/min after 20 min of reperfusion without and with adrenaline, respectively. When halothane (0.5%) was given intermittently during the arrest, the postarrest ATP averaged 8.23 ± 0.62 μmol/g dry wt ($P < 0.001$), which improved to 16.01 ± 0.90 μmol/g dry wt after 20 min of reperfusion and subsequent administration of adrenaline. Under these experimental conditions, aortic flow during reperfusion was 20.17 ± 4.49 mL/min ($P < 0.01$), and this improved to 37.67 ± 4.49 mL/min on administration of adrenaline. Similar tendencies were observed with 1% and 1.5% halothane. Our results indicate that halothane does not preserve myocardial ATP during normothermic arrest and ischemia. However, the use of halothane was associated with improved recovery of ATP content and systolic reserve after reperfusion. Hearts not receiving halothane did not restore their ATP content and had depressed systolic reserve. These observations cannot be explained by the effect of halothane on global myocardial mechanics, and the beneficial effect of halothane may be related to the prevention of the reperfusion injury.

(Anesth Analg 1991;73:711–9)

Reperfusion of the ischemic heart is associated with a rapid gain in intracellular calcium, the extent of which is related to the severity and duration of ischemia (1,2). In turn, the degree of ischemic damage has a negative correlation with mechanical recovery; and interventions limiting calcium accumulation and depletion of myocardial high-energy phosphates (HEP), such as pretreatment with the calcium-blocking agent verapamil, have been shown to protect the ischemic myocardium (3,4).

Although not chemically related to other drugs that alter myocardial calcium fluxes, halothane does affect the intracellular calcium in the myocardium. The negative inotropic actions of halothane have been attributed to a reduction in the slow inward current for calcium (5–9); and furthermore, halothane inhibits the abnormal accumulation of tissue calcium associated with ischemia and reperfusion (10). From the above, it was thought reasonable to speculate that halothane will protect the myocardium against ischemic damage; therefore, the effects of different concentrations of halothane were studied on the func-

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Supported by the Medical Research Council and Harry Crossley Foundation.

Accepted for publication August 1, 1991.

Address correspondence to Dr. Coetzee, Department of Anesthesiology, University of Stellenbosch Medical School, P.O. Box 63, Tygerberg 7505, South Africa.

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0003-2999/91/$3.50

tional and metabolic recovery of isolated rat hearts after exposure to hypothermic or normothermic cardioplegic arrest. Specifically, answers were sought to the following questions: (a) Does halothane protect the myocardium against ischemic damage? (b) If so, can our results suggest a specific mechanism?

Methods

The experimental protocol was approved by the institutional ethics committee and animals were cared for according to national and institutional guidelines. Male Wistar rats (weight, ~200 g) were anesthetized with intraperitoneal pentobarbital (25–30 mg/rat). The hearts were removed, arrested in cold Krebs-Henseleit buffer (4°C), and the aortas were mounted onto an aortic cannula. Initially, the hearts were retrogradely perfused for 10 min during which time the pulmonary vein was cannulated. Afterwards, the atrium was filled from a reservoir providing a constant filling pressure (15 cm H_2O), and the heart was perfused in the working mode for 20 min (ejection pressure, 100 cm H_2O) (11,12). The composition of the perfusate was (in mmol/L): NaCl, 124; KCl, 4.93; $CaCl_2$, 1.25; $MgCl_2$, 1.62; Na_2SO_4, 0.6; KH_2PO_4, 1.23; $NaHCO_3$, 26; glucose, 10. The perfusate was oxygenated with 95% O_2/5% CO_2 and the temperature was kept constant at 37°C.

After 20 min of perfusion in the working mode, hearts were arrested with Plasmalyte B (Sabax, South Africa) to which $CaCl_2$ (1.25 mmol/L) and KCl (25 mmol/L) were added (final composition in mmol/L: Na^+, 130; K^+, 29; Cl^-, 109; HCO_3^-, 28; Ca^{2+}, 1.25; pH, 7.4; osmolality, 273 mOsm). The cardioplegic solution was gassed with 95% O_2/5% CO_2. The initial perfusion was maintained for 3 min at a pressure of 40 mm Hg, and afterwards the cardioplegic solution was administered for 1 min at 10-min intervals using the same perfusion pressure (13).

After the arrest period, hearts were switched to another perfusion system and reperfused with Krebs-Henseleit buffer at 37°C. Initially, reperfusion was in the retrograde mode for 10 min followed by 20 min of perfusion in the working mode. Adrenaline (10^{-6} mol/L) was administered during the last 10 min of reperfusion in the normothermic group. When administered, halothane was vaporized from a calibrated vaporizer (Drägerwerk, Germany) using a constant fresh gas flow during all the experiments.

Measurements of aortic output (AO), heart rate (HR), coronary flow (CF), and peak systolic pressure (PSP) were registered at the following times: (a) immediately before the heart was arrested; (b) after arrest and 20 min of reperfusion, and (c) at the end of the experiment, i.e., after the administration of adrenaline (in the normothermic group only). Stroke volume, kinetic (W_k), pressure (W_p), and total work (W_t) were calculated as described before (13). Hearts were freeze-clamped at one of the following times: (a) before arrest, (b) at the end of the arrest period, or (c) after reperfusion (in the normothermic group, after reperfusion and subsequent perfusion with adrenaline). The tissue was stored in liquid nitrogen until extraction of HEP. Adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and creatine phosphate (CP) were analyzed by ion-pair reversed-phase high-performance liquid chromatography (14). As described above, all hearts were perfused for a 30-min control period before arrest. This was followed by cardioplegia-induced arrest (40 or 60 min) and by reperfusion for 30 min. The study had two subdivisions:

A. Hypothermic arrest. In this group, the arrested hearts were maintained for 60 min at 20°C with the aid of a surrounding waterbath.
   A1: Control, no halothane.
   A2: Hearts received 0.5% or 1.5% halothane *in the cardioplegic solution only* (i.e., during the intermittent administration of the cardioplegic solution).
   A3: Hearts received 0.5% or 1.5% halothane, during the last 10 min of the control (before arrest) period and a similar concentration throughout the reperfusion period.

B. Normothermic arrest. In this group, hearts were arrested with the cardioplegic solution for 40 min at 37°C. These groups were similar to the A groups except that three concentrations of halothane were studied: 0.5%, 1.0%, and 1.5%. Furthermore, during the last 10 min of the reperfusion period, hearts were subjected to adrenaline (10^{-6} mol/L) to evaluate their inotropic potential.
   B1: Control, no halothane.
   B2: Hearts received halothane in the cardioplegic solution only.
   B3: Hearts received 0.5%, 1.0%, or 1.5% halothane before and after arrest (administered as in A3).

In addition to the above protocols, 18 hearts were subjected to similar before-arrest conditions of 10-min passive retrograde perfusion and 20-min working heart mode. At the end of this period, function was quantified and hearts were freeze-clamped for HEP determination. These values were used as control references for certain sections of the experiments.

Statistical analysis was performed with the paired and unpaired *t*-test. For the paired *t*-test, normal distribution of data was checked with the Sharpiro-Francia W test (15). When the unpaired *t*-test was

Table 1. Hemodynamics Before and After Hypothermic (20°C) Arrest

	HR (beats/min)	AO (mL/min)	CF (mL/min)	PSP (mm Hg)	W_t (mW)
A1. Control (no halothane) (n = 18)					
Before	296 ± 9.26	46.6 ± 4.81	16.40 ± 0.60	101.00 ± 1.00	14.49 ± 0.61
After	290 ± 13.21	23.1 ± 5.00^{aa}	11.90 ± 1.40^{a}	91.00 ± 2.62^{aa}	7.25 ± 1.34^{a}
A2. Halothane in cardioplegia					
0.5% Halothane (n = 8)					
Before	302 ± 19.80	45.23 ± 2.30	15.42 ± 1.92	104.00 ± 1.82	14.06 ± 1.51
After	287 ± 18.00	25.80 ±3.50^{aaa}	13.11 ± 1.82^{aa}	91.24 ± 3.62^{aaa}	8.22 ± 1.72^{aaa}
1.5% Halothane (n = 11)					
Before	263 ± 36.11	42.00 ± 1.60	17.11 ± 1.93	91.02 ± 3.60	14.21 ± 1.91
After	256 ± 52.00	25.50 ± 2.60^{aaa}	16.33 ± 3.31	93.40± 6.41^{aaa}	8.71 ± 2.20^{aa}
A3. Halothane before and after arrest					
0.5% Halothane (n = 6)					
Before	258 ± 15.62	38.09 ± 1.40	11.61 ± 2.02	97.11 ± 2.02	11.61 ± 0.75
After	259 ± 14.21	23.80 ± 0.90^{aaa}	12.34 ± 0.90	87.41 ± 1.00^{aa}	7.22 ± 0.45^{aa}
1.5% Halothane (n = 6)					
Before	244 ± 7.00	14.50 ± 3.70	12.34 ± 0.70	82.19 ± 5.00	4.85 ± 0.67
After	247 ± 26.18	13.28 ± 3.80	9.63 ± 1.80	78.18 ± 9.00	2.50 ± 0.87^{a}

HR, heart rate; AO, aortic flow, CF, coronary flow; PSP, peak systolic pressure; W_t, total work; Before, before cardioplegic arrest; After, after arrest and reperfusion.

General hemodynamic variables for experiments with cardioplegia conducted at 20°C. (Cardiac arrest for 60 min.) Values are the mean ± SEM for the number of experiments indicated. Statistical analysis was performed between the before- and after-arrest values for each halothane concentration.

$^{a}P < 0.05$.

$^{aa}P < 0.01$.

$^{aaa}P < 0.0001$.

applied, variances were evaluated and if unequal, the Welch test was applied (16). A probability of 5% was considered significant.

Results

Group A

Before-arrest and after-arrest data (Table 1) from the control study (no halothane, A1) were compared with data from the group in which halothane was added to the cardioplegia (A2).

In group A1, the AO, CF, PSP, and W_t were reduced after the arrest when compared with the before-arrest values. The HR remained constant. In group A2, comparison of before-arrest data (A2, Before) did not differ from the data (A1, Before) in the control group. Data obtained after the arrest (A2, After) also did not differ from data (A1, After) from group A1.

Comparison of before- and after-arrest data (A2) demonstrated a significant reduction in AO, PSP, CF, and W_t for the after-arrest group with the use of 0.5% halothane. Similar results were obtained for 1.5% halothane except that the CF did not differ. No differences were shown when the after-arrest values for 0.5% and 1.5% halothane were compared.

In the 0.5% halothane group (group A3), AO, PSP, and W_t were significantly less for the after-arrest values compared with the before-arrest values. With 1.5% halothane only, the after-arrest W_t was reduced.

Group B

As in group A, the control group (B1, no halothane) was compared stepwise with the group receiving halothane in the cardioplegia (B2) (Table 2, Figures 1 and 2).

In group B1, all the values (HR, AO, CF, PSP, and W_t) (Table 2, B1) were significantly reduced after the period of elective normothermic arrest. Only one of the six hearts studied in this series was able to produce AO during the reperfusion phase. When adrenaline (10^{-6} mol/L) was administered, all values improved significantly compared with the after-arrest phase (without adrenaline); however, although values were numerically less than before-arrest values, only the AO was significantly less.

When 0.5% halothane was used in group B2, the after-arrest PSP, AO, and W_t were less compared with before-arrest values (Table 2, B2). However, AO, CF, and W_t were significantly higher than those obtained in group B1 (no halothane). When adrena-

Table 2. Hemodynamics Before and After Normothermic (37°C) Arrest

	HR (beats/min)	AO (mL/min)	CF (mL/min)	PSP (mm Hg)	W_t (mW)
B1. Control (no halothane) ($n = 6$)					
Before	284 ± 10.27	43.62 ± 2.40	14.58 ± 1.10	104.50 ± 1.41	13.61 ± 0.67
After	124 ± 39.90^{aa}	1.80 ± 1.80^{aaa}	9.50 ± 1.34^{a}	53.67 ± 15.60^{a}	1.63 ± 0.72^{aaa}
Adrenaline	335 ± 27.50^{bb}	22.01 ± 8.36^{b}	17.12 ± 2.36^{b}	99.60 ± 6.49^{b}	9.43 ± 2.50^{bb}
B2. Halothane in cardioplegia					
Halothane 0.5% ($n = 5$)					
Before	288 ± 10.54	45.92 ± 1.12	16.50 ± 0.55	99.29 ± 1.43	14.32 ± 0.81
After	317 ± 16.02	$20.17 \pm 4.98^{aa}_{ccc}$	15.67 ± 1.30^{c}	88.92 ± 1.96^{aa}	$6.85 \pm 1.47^{aa}_{c}$
Adrenaline	408 ± 12.07^{b}	37.67 ± 4.49^{b}	18.42 ± 1.27	96.50 ± 2.17^{b}	12.49 ± 1.47^{b}
Halothane 1.0% ($n = 6$)					
Before	293 ± 12.57	44.00 ± 1.85	15.21 ± 0.56	98.00 ± 2.19	13.12 ± 0.64
After	266 ± 13.21^{c}	$19.00 \pm 3.10^{aa}_{c}$	$12.00 \pm 85^{aa}_{c}$	89.45 ± 1.40^{aa}	$6.19 \pm 0.77^{aaa}_{cc}$
Adrenaline	375 ± 6.42^{bbb}	$43.41 \pm 2.42^{bbb}_{c}$	$18.26 \pm 0.47^{bbb}_{c}$	99.62 ± 0.82^{bbb}	$13.91 \pm 0.74^{bbb}_{c}$
Halothane 1.5% ($n = 5$)					
Before	302 ± 9.15	42.50 ± 2.61	17.26 ± 0.43	98.50 ± 2.28	13.42 ± 0.89
After	313 ± 23.22	28.35 ± 2.48^{aaa}	17.00 ± 0.45	88.20 ± 1.62^{aa}	9.09 ± 0.64^{aa}
Adrenaline	394 ± 11.45^{b}	$42.42 \pm 2.38^{bb}_{ccc}$	20.10 ± 0.46^{bb}	100.80 ± 1.32^{bbb}	$14.30 \pm 0.70^{bbb}_{c}$
B3. Halothane before and after arrest					
Control (no halothane)^{f} ($n = 18$)					
	321 ± 5.70	43.24 ± 1.11	16.67 ± 0.32	96.19 ± 0.87	13.23 ± 0.37
Halothane 0.5% ($n = 10$)					
Before	299 ± 14.21	28.70 ± 1.84	14.10 ± 0.74	88.10 ± 1.02	8.52 ± 0.51
After	286 ± 15.80	6.08 ± 2.03^{aaa}	18.60 ± 2.16^{aaa}	80.21 ± 1.26^{aaa}	3.37 ± 0.46^{aaa}
Adrenaline	$374 \pm 11.82^{bbb}_{eee}$	$39.65 \pm 3.49^{bbb}_{e}$	17.38 ± 0.60^{e}	$101.80 \pm 2.42^{bbb}_{eee}$	$13.43 \pm 1.22^{bbb}_{c}$
Halothane 1% ($n = 4$)					
Before	297 ± 17.77	19.20 ± 2.50^{ddd}	15.50 ± 0.31	84.20 ± 1.25^{ddd}	5.83 ± 0.46^{ddd}
After	287 ± 19.30	1.75 ± 1.44^{aaa}	15.00 ± 1.08	73.30 ± 4.05^{a}	2.78 ± 0.40^{aa}
Adrenaline	$374 \pm 25.60^{b}_{e}$	$32.25 \pm 4.50^{bbb}_{e}$	$18.63 \pm 0.94^{b}_{e}$	$98.00 \pm 2.42^{bb}_{eee}$	$11.39 \pm 1.30^{bb}_{ee}$
Halothane 1.5% ($n = 4$)					
Before	284 ± 18.04	7.25 ± 3.63^{ddd}	16.50 ± 2.21^{ddd}	80.75 ± 1.93^{ddd}	4.32 ± 0.80^{ddd}
After	142 ± 83.62	0.00 ± 0.00^{a}	10.63 ± 2.51	31.50 ± 19.06^{a}	0.83 ± 0.49^{aa}
Adrenaline	$379 \pm 8.20^{b}_{e}$	$22.69 \pm 3.06^{bbb}_{eee}$	18.12 ± 2.18	$91.25 \pm 1.03^{b}_{ee}$	$8.60 \pm 1.20^{bbb}_{e}$

HR, heart rate; AO, aortic flow; CF, coronary flow; PSP, peak systolic pressure; Wt, total work; Before, values obtained before cardioplegic arrest; After, values obtained after cardioplegic arrest. Hemodynamics from experiments with cardioplegia conducted at 37°C. (Cardiac arrest for 40 min.). Values are mean ± SEM. Statistical comparisons are indicated as follows:

[a] Between Before and After values.
[b] Between After and Adrenaline values.
[c] Comparison similar group B1 to group B2 values.
[d] Control and Before values for group B3.
[e] Before and Adrenaline in group B3.
[f] Mean values for a series of 18 hearts perfused for 30 min under control conditions.
a,b,c,d,e = $P < 0.05$.
aa, bb, cc, dd, ee = $P < 0.01$.
aaa, bbb, ccc, ddd, eee = $P < 0.001$.

line was used, all the variables except CF improved significantly when compared with the before-arrest values (without adrenaline).

Halothane (1.0%) was associated with a significant reduction in AO, CF, PSP, and W_t when after-arrest values were compared with before-arrest values. Adrenaline increased all the variables; and the AO, CF, and W_t registered after halothane was added to the cardioplegia were better than the values obtained in group B1.

The use of 1.5% halothane was associated with reduced AO, PSP, and W_t when before-arrest values were compared with after-arrest values. Adrenaline improved all the variables when compared with no-adrenaline values, whereas the AO and W_t were significantly better than that of the B1 group receiving no halothane.

Regardless of the concentration of halothane used, after arrest values in group B3 showed a reduction in AO, CF, PSP, and W_t (Table 2, B3). Adrenaline improved all the values significantly when compared with after-arrest values.

For all three concentrations of halothane, HR, AO, PSP, and W_t were significantly higher in the adrenaline group when compared with the before-arrest values.

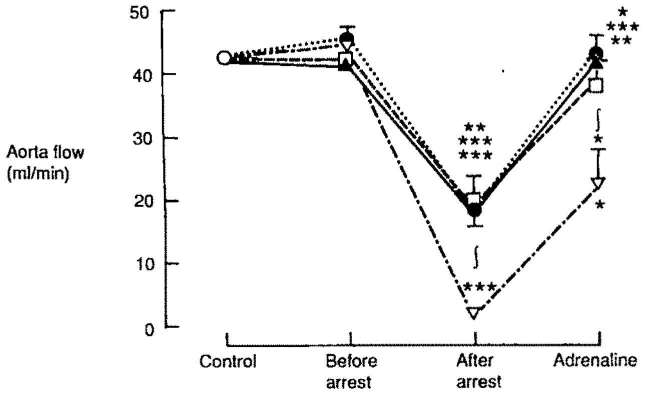

Figure 1. Experiment B2. Aortic flow before and after cardioplegic arrest (0.5%–1.5% halothane administered during cardioplegic arrest). Adrenaline (10^{-6} mol/L) administered during the last 10 min of reperfusion. Experiments were conducted at 37°C and arrest was maintained for 40 min. Statistical analyses were performed between the before- and after-arrest values (*); after arrest and adrenaline values (*); control (no halothane) and the hearts receiving halothane (∫). ▽, Control (no halothane, $n = 5$); □, 0.5% halothane, $n = 5$; ●, 1% halothane, $n = 5$; ▲, 1.5% halothane, $n = 5$. Values are mean ± SEM. ∫*$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.

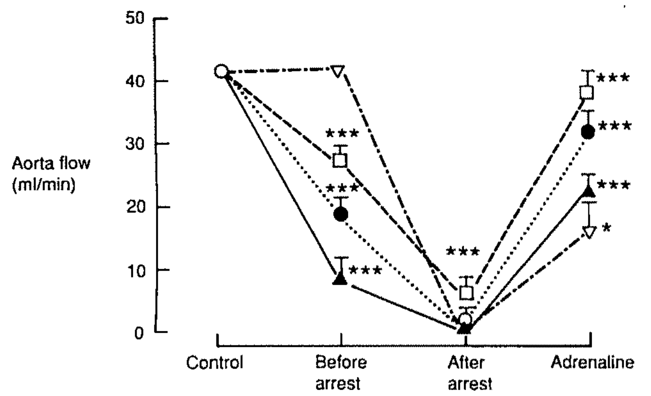

Figure 2. Experiment B3. Effect of halothane (0.5%–1.5%) administered before and after cardioplegic arrest on aortic flow. Experiments were conducted at 37°C and arrest was maintained for 40 min. Statistical analyses were performed between control vs before arrest (*), before vs after arrest (*), after arrest and the administration of adrenaline (*). In all three statistical analyses, the values obtained after arrest differed from that obtained before arrest. ▽, Control (no halothane, $n = 6$); □, 0.5% halothane ($n = 10$); ●, 1% halothane ($n = 4$); ▲, 1.5% halothane ($n = 4$). Values are mean ± SEM. *$P < 0.05$. ***$P < 0.001$.

Tissue High-Energy Phosphates

Halothane, when administered either during or before and after hypothermic (20°C) cardioplegia, had no effect on tissue high-energy phosphate levels as measured at the end of the reperfusion period (Table 3, A, Figure 3).

Normothermic arrest for 40 min (without halothane) caused a reduction in myocardial ATP and in CP concentrations. Control values for ATP and CP (obtained after 10-min retrograde and 20-min working heart perfusion) were 23.04 ± 0.75 and 20.69 ± 0.42 μmol/g dry wt, respectively. The after-arrest values (at 37°C for 40 min) were ATP 9.05 ± 0.70 μmol/g dry wt and CP 4.53 ± 0.34 μmol/g dry wt, respectively. The ATP values remained depressed after reperfusion and stimulation with adrenaline, whereas the CP content increased (Table 3, B1, C1).

Addition of halothane during the before-arrest period only (B2) caused a marked depression in tissue ATP and CP levels at the end of the cardioplegic period when compared with those of hearts not receiving halothane (B1) or of hearts receiving halothane during the cardioplegic period (B3). However, no significant differences were observed between tissue high-energy phosphates from hearts not receiving halothane (B1) and from those receiving halothane during the cardioplegic period (B3).

However, with reperfusion and after adrenaline stimulation, hearts subjected to halothane (regardless of concentration) improved their ATP concentration (Table 3, C2, C3, Figure 4). Hearts not receiving halothane did not increase their ATP, and there was a significant difference between ATP concentration of hearts not receiving halothane (C1) and those that did receive halothane (C2, C3). The mode of administration of halothane did not affect the results, and the high-energy phosphate contents of hearts receiving halothane during the cardioplegic period (C2) were similar to those having received halothane before and after arrest (C3).

Discussion

Recent research has confirmed that during an ischemic incident, intracellular calcium levels not only increase above resting levels (17–20) but changes in intracellular distribution of calcium also occurs (20). This increase in intracellular calcium could result from an increased Ca^{2+} influx or from a decreased Ca^{2+} eflux, and although most evidence favors influx through the voltage-dependent Ca^{2+} channel (21), other mechanisms such as the Na^{+}/Ca^{2+} exchange may also be involved (22, 23). Halothane, by virtue of its inhibitory effects on the slow inward current for calcium (5–9), should therefore protect the myocardium against ischemic damage. Indeed, the beneficial effect of halothane on intracellular accumulation of calcium during ischemia and the calcium paradox has already been reported (10).

Results obtained in this study showed that in hearts subjected to *hypothermic* arrest, halothane did not improve protection over and above that afforded by hypothermia and oxygenated cardioplegia. Research from our laboratory indicated that oxygenated crystalloid cardioplegia and hypothermia effectively protect the isolated arrested rat heart against ischemic damage, as indicated by preservation of normal ultrastructure and HEP, as well as functional recovery during reperfusion (13, 24). Although our experimen-

Table 3. Tissue High-Energy Phosphates

	ATP	ADP	AMP	CP
A. Cardiac arrest at 20°C for 60 min (samples taken at end of reperfusion)				
A1. Control (no halothane) ($n = 7$)				
	23.04 ± 0.75	6.16 ± 0.25	2.27 ± 0.34	20.69 ± 3.42
A2. Halothane in cardioplegia ($n = 6$)				
H 0.5%	15.80 ± 1.91	7.41 ± 0.93	2.92 ± 0.56	12.93 ± 0.64
H 1.5%	20.83 ± 5.11	4.71 ± 1.54	1.43 ± 1.22	17.51 ± 3.50
A3. Halothane before and after arrest ($n = 10$)				
H 0.5%	18.71 ± 3.52	7.80 ± 0.71	2.74 ± 0.41	20.11 ± 1.00
H 1.5%	17.20 ± 4.41	7.91 ± 0.93	2.71 ± 0.50	14.12 ± 1.90
B. Cardiac arrest at 37°C for 40 min (samples taken at end of cardioplegia, without reperfusion)				
B1. Control (no halothane) ($n = 4$)				
	9.34 ± 1.12	6.33 ± 0.56	5.59 ± 0.64	4.81 ± 0.68
B2. Halothane before arrest only ($n = 6$)				
H 0.5%	4.02 ± 0.38[aa]	4.27 ± 0.20[a]	10.42 ± 0.71[aaa]	3.94 ± 0.40
H 1.0%	3.35 ± 0.67[aa]	4.12 ± 0.34[a]	10.47 ± 1.13[aa]	3.60 ± 0.45
H 1.5%	4.53 ± 0.84[a]	4.14 ± 0.68[a]	9.04 ± 1.17	3.65 ± 0.61
B3. Halothane in cardioplegia				
H 0.5% (8)	8.23 ± 0.62	5.62 ± 0.31	9.68 ± 1.52	6.29 ± 0.76
H 1.0% (10)	11.71 ± 1.91	5.79 ± 0.46	5.41 ± 0.72	9.82 ± 2.83
H 1.5% (4)	8.80 ± 0.75	5.81 ± 0.38	6.99 ± 1.41	5.87 ± 0.85
C. Cardiac arrest at 37°C for 40 min (samples taken at end of reperfusion)				
C1. Control (no halothane) ($n = 6$)				
	9.57 ± 0.62	3.53 ± 0.25	2.39 ± 0.20	10.57 ± 0.92
C2. Halothane in cardioplegia ($n = 5$)				
H 0.5%	16.01 ± 0.90[aa]	7.47 ± 0.28[aaa]	2.27 ± 0.20	17.00 ± 0.80[aaa]
H 1.0%	14.08 ± 0.29[aa]	7.97 ± 0.31[aaa]	2.56 ± 0.20	13.22 ± 0.23[a]
H 1.5%	14.47 ± 0.67[aaa]	7.22 ± 0.32[aaa]	2.59 ± 0.23	14.47 ± 0.71[aa]
C3. Halothane before and after arrest ($n = 6$)				
H 0.5%	13.45 ± 0.32[aaa]	6.43 ± 0.20[aaa]	2.63 ± 0.25	12.93 ± 0.35[a]
H 1.0%	14.10 ± 0.70[aaa]	6.42 ± 0.31[aaa]	2.37 ± 0.52	14.16 ± 0.89[a]
H 1.5%	16.28 ± 1.57[aaa]	5.42 ± 0.26[aaa]	3.18 ± 0.32	12.66 ± 0.9

ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; CP, creatine kinase; H, halothane.

Values in mol/g dry wt are mean ± SEM for the number of samples indicated. Comparison was done between each variable and the control within the group.

[a] Comparison between control and halothane values within each group.

[a] $P < 0.05$.

[aa] $P < 0.01$.

[aaa] $P < 0.001$.

tal model allows for effective myocardial hypothermia throughout the arrest period, this may not be the case in clinical practice. Also, in the current experiments, normal rat hearts were used, whereas ischemic incidents do occur during the perioperative period in, for instance, patients scheduled for coronary artery bypass surgery (25). Therefore, we elected to repeat the experiments in rat hearts that have been subjected to partially reversible ischemic damage.

Hearts subjected to *normothermic cardioplegic* arrest for 40 min were found to be a suitable model, as a significant reduction in tissue HEP occurred (as measured after the arrest and at the end of reperfusion). This was associated with a significant decline in functional recovery during reperfusion (only 1 of 6 hearts produced AO). However, despite the above changes, these hearts still had the potential for *partial* recovery as indicated by their response to adrenaline (Table 2). From the experiments in which halothane was administered to normothermic arrested hearts, the following observations were made:

1. Halothane did not protect against the decline in tissue ATP during normothermic arrest. The ATP levels at the end of the arrest were of similar magnitude as those measured in hearts not receiving halothane. In hearts receiving halothane before they were arrested, ATP tended to be less than that in hearts not receiving halothane or in hearts subjected to halothane in the cardioplegia. The finding that halothane, when administered before cardioplegic arrest, depressed myocardial ATP and CP was unexpected, and our data are insufficient to explain this.
2. Regardless of the concentration of halothane, hearts receiving halothane either during the car-

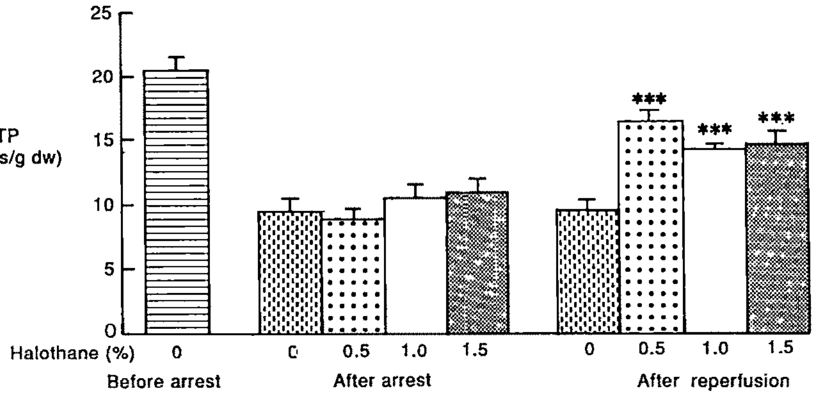

Figure 3. Myocardial ATP (μmol/g dry wt) during control, after arrest, and after reperfusion in hearts receiving halothane during cardioplegia only. Arrest was maintained for 40 min at 37°C and values are mean ± SEM ($n = 6$). Statistical analyses were performed between control (0% halothane, before arrest) and each of the after-arrest values: 0% halothane after reperfusion with the 0.5%–1.5% halothane groups after reperfusion. ***$P < 0.001$.

dioplegic period or before and after arrest improved the tissue ATP and CP toward the end of the experiment, i.e., after reperfusion and stimulation with adrenaline. Hearts not receiving halothane failed to improve their ATP.

3. Although myocardial function was depressed after the arrest in all the hearts, those receiving halothane had a better systolic reserve (as shown by the response to adrenaline) compared with hearts not receiving halothane, which failed to normalize their function on inotropic intervention.
4. The finding that halothane, when given intermittently during cardioplegic arrest, caused similar functional and metabolic recovery as when administered during reperfusion, suggests that sufficient amounts of the anesthetic partitioned into myocardial cellular membranes or endogenous lipids, or both, (26) to be effective during reperfusion. Considering the small total dose of halothane administered during cardioplegic arrest only, it can be speculated that halothane indeed has a powerful effect in protecting the heart against the detrimental effects of ischemia and/or reperfusion.
5. The absence of a dose-response curve for the protection of ATP and function, as observed for halothane, cannot be explained by our results. However, it may well be that the effect of halothane is such that at 0.5% the maximum protection potential has already been realized. If this speculation is correct, a dose-response curve could be expected for concentrations less than 0.5% halothane, and this possibility is currently being investigated in our laboratory.

Beneficial effects of volatile anesthetics on the ischemic or hypoxic heart have also been observed by others. Enflurane, for instance, was shown to improve recovery of peak pressure and ATP during reperfusion (27), whereas both halothane and isoflurane decreased the incidence of ventricular tachycardia and fibrillation and increased the time in sinus rhythm occurring during hypoxia and reoxygenation (28). The mechanism of this protective action is not yet clear, and a number of possibilities should be considered.

Halothane does decrease developed myocardial tension (29,30), heart rate, and the rate of ATP consumption (31,32). The results obtained in the present study also showed that halothane has a negative inotropic and chronotropic effect on the isolated perfused heart (Tables 1 and 2). A combination of these factors could prevent or retard the rate of ATP breakdown and hence protect the after-arrest function. Indeed, the effect of halothane on global myocardial function has been suggested as one of the methods by which halothane protected the isolated guinea pig heart against hypoxia (28). Our data suggest that halothane, when given before the heart was arrested, did not protect against ATP breakdown during ischemia (Table 3). It therefore appears unlikely that a depression of global cardiac function caused by halothane given before the ischemic episode is responsible for the improved systolic function after the arrest. During hypoxia, calcium-activated myocardial contracture occurs (33), and this effect has been minimized by the use of halothane (28). Although we did not determine static diastolic compliance, our results suggest that the effect of halothane on diastolic compliance (during ischemia) is insufficient to explain our findings as it is expected that diastolic contracture would reduce the ATP content at the end of the arrest. We could not show a difference in ATP content at the end of the arrest when hearts receiving halothane were compared with those not receiving halothane. The effect of halothane on coronary flow (34) is also unlikely to explain our results as our model did not have continuous coronary flow during arrest.

In our ischemic model, halothane appears to have relatively little effect on biochemical events during normothermic arrest: halothane administered during cardioplegic arrest did not retard ATP breakdown (Table 3), although the tendency of CP levels to

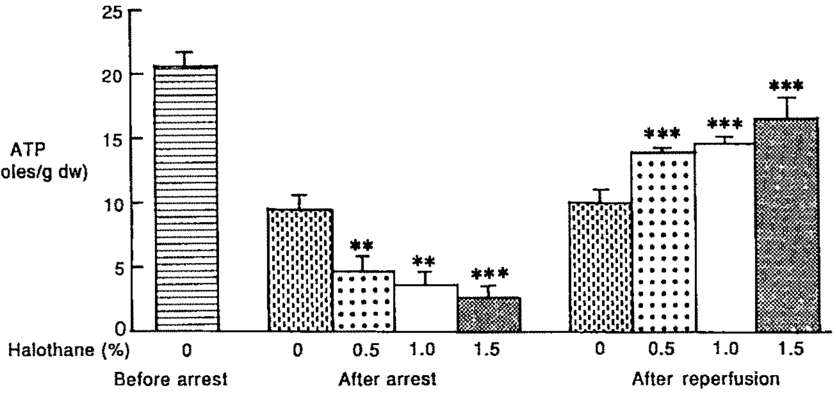

Figure 4. Myocardial ATP (µmol/g dry wt) after arrest and at the end of the experiment in hearts receiving halothane before and after the cardioplegia. Arrest was maintained for 40 min at 37°C and values are mean ± SEM ($n = 6$). Statistical analyses were performed between control (i.e., 0% halothane) and the steps containing halothane for that particular subgroup. $^{**}P < 0.01$. $^{***}P < 0.001$.

increase is suggestive of some degree of protection against ischemic damage. However, in view of the restoration of ATP to control (before arrest) levels and myocardial functional recovery during reperfusion and adrenaline, it appears as if halothane exerts its protective effects mainly during reperfusion.

It is well established that reperfusion damage is associated with intracellular Ca^{2+} overloading (2,35). Because of the inhibitory action of halothane on the slow inward current of Ca^{2+} (5–9) and the role of this channel in ischemia-induced Ca^{2+} overloading (2,35, 36), the possibility exists that halothane exerts its protective effect by inhibition of excessive intracellular Ca^{2+} accumulation during reperfusion. There is indirect evidence supporting this view:

1. Halothane has been shown to inhibit the calcium paradox in the isolated heart (10).
2. Reperfusion of the myocardium after an ischemic incident increases intracellular Ca^{2+} (2,35,37). This will interfere with intracellular high-energy phosphate homeostasis resulting from the sequestration of calcium into mitochondria and the depression of oxidative phosphorylation (38).
3. Calcium entry blockers (e.g., verapamil, nifedipine) have been shown to alleviate ischemic injury (2,3).
4. In hearts subjected to normothermic cardioplegic arrest without halothane (in our experiments), myocardial stunning (39) was observed. There is evidence that this is due to free radical formation and subsequent Ca^{2+} overloading rather than ATP depletion (40). Furthermore, experimental studies have indicated that halothane improved recovery of contractile function in the stunned myocardium (41) and reduced myocardial infarct size in dogs (42).

In conclusion, halothane prevents prolonged myocardial dysfunction after ischemia, and our results indicate that this beneficial effect occurs mainly during reperfusion. We speculate that this effect is most probably due to the ability of halothane to prevent postischemic reperfusion damage in general and calcium overload in particular.

We thank Renee Winterbach and Annemie Jordaan for technical assistance and Petro Hanekom for typing the manuscript.

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Persistent Cardiac Arrhythmias in Pediatric Patients: Effects of Age, Expired Carbon Dioxide Values, Depth of Anesthesia, and Airway Management

Norbert Rolf, MD, and Charles J. Coté, MD

Department of Anaesthesia, Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts

The presence of persistent arrhythmias was correlated with hypercarbia (end-tidal $CO_2 \geq 55$ mm Hg for ≥ 60 s). A continuous strip chart recording of oxygen saturation, a capnogram, and an electrocardiogram were obtained from 402 children. No episodes of arrhythmia occurred in 153 patients younger than 2 yr compared with 24 patients 2 yr of age or older ($P = 0.0001$). Older patients whose airways were managed via a mask had a higher incidence (13.2% [21 of 159 patients]) than tracheally intubated patients (3.3% [3 of 90 patients]) ($P = 0.01$). In older patients whose tracheas were intubated, hypercarbia was associated with arrhythmia in 1 of 20 hypercarbia episodes. Seven of 16 patients with hypercarbia, whose airways were managed via a mask, had an arrhythmia ($P = 0.0014$); in eight, arrhythmias were associated with light anesthesia; in seven, arrhythmias were not associated with either hypercarbia or light anesthesia. Arrhythmias developed in 13 of 55 patients 2 yr old or older whose airways were managed via a mask and who were undergoing orchiopexy or herniorrhaphy as compared with 1 of 30 tracheally intubated patients ($P = 0.016$). There was a higher incidence of arrhythmias during halothane anesthesia compared with that during all other techniques ($P = 0.035$). The authors conclude that the incidence of arrhythmias is extremely low in infants younger than 2 yr. Hypercarbia is associated with arrhythmias in pediatric patients whose airways are managed via a mask but not in patients whose tracheas are intubated. Light anesthesia, as evidenced by movement, increased arterial blood pressure, and heart rate, may be an equally important cause of arrhythmia particularly during procedures with wide variations in the strength of the surgical stimulus. Capnographic monitoring was not associated with a change in the incidence of arrhythmias.

(Anesth Analg 1991;73:720–4)

The incidence of cardiac arrhythmias during general anesthesia is as high as 60% in adult patients (1–4). A variety of factors may account for these arrhythmias, such as the effects of anesthetics, the response to surgical or anesthetic stimuli, respiratory acidosis, cardiac reflexes, medications, exogenous or endogenous epinephrine, and preexisting diseases affecting cardiac impulse initiation or conduction (1–4). The purpose of this study was to examine the association between hypercarbia and persistent cardiac arrhythmias in pediatric patients undergoing a variety of routine surgical procedures and to determine if the monitoring of peak expired carbon dioxide (P_{ECO_2}) influenced the incidence of arrhythmias.

Methods

Data were collected simultaneously from a single-blind, randomized, prospective protocol examining the efficacy of pulse oximetry and capnography on the incidence of desaturation episodes in anesthetized pediatric patients (results reported elsewhere) (5). This study focused on factors associated with persistent ventricular arrhythmias, particularly hypercarbia. The study protocol was approved by the Subcommittee on Human Studies of the Massachusetts General Hospital, and informed written consent was obtained for all patients. Children who were ASA physical status I–IV and who were scheduled for operation under general anesthesia were eligible for study; however, patients with cyanotic congenital heart defects and those scheduled for bronchoscopy were excluded. The anesthetic management, including the type of airway management (face mask or endotracheal tube), was left to the discretion of the anesthesia team. All patients were monitored with a precordial stethoscope, automated oscillometric

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Supported by grants from Nellcor Inc., Hayward, California; the Anesthesia Patient Safety Foundation, Park Ridge, Illinois; and the Humboldt Foundation, Bonn, Germany.
Accepted for publication July 30, 1991.

Address correspondence to Dr. Coté, Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114.

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0003-2999/91/$3.50

blood pressure measurement (Dinamap), electrocardiogram (lead II), temperature, inspired oxygen concentration, pulse oximetry, and capnography (N 1000, Nellcor, Hayward, Calif.). Patients were randomly assigned to one of four monitoring categories: (a) oximetry and capnography, (b) only oximetry, (c) only capnography, and (d) neither oximetry nor capnography data nor alarms available to the anesthesia team. For purposes of this study, patients were divided into two alarm categories: capnography data available and capnography data unavailable to the anesthesia team.

In patients whose airways were managed via a face mask, the sample for capnography was obtained at the right-angle connector of the breathing system (circle or Mapleson D). When possible, a special endotracheal tube with a built-in sampling line for carbon dioxide, which allowed gas samples to be obtained from the tip of the endotracheal tube, was used in patients whose tracheas were intubated with an endotracheal tube with an internal diameter smaller than 4.5 mm. When an endotracheal tube with an internal diameter larger than 4.5 mm was used or when there was a problem with inserting a special endotracheal tube or with obtaining a sample from the built-in sampling port (obstruction due to secretions), the gas sample for capnography was obtained at the right-angle connector of the breathing circuit. To assess the reliability of P_{ECO_2} samples obtained at the right-angle connector in small patients who did not have special sampling tubes inserted, we compared measured P_{ECO_2} values at both locations in 10 patients.

A continuous strip chart recording of the oxygen saturation, the plethysmographic output of the pulse oximeter, the capnogram, and the electrocardiogram was obtained for each patient from the time anesthesia was induced to the time the patient was transferred to the recovery room. The oxygen saturation channel of the strip chart recorder was calibrated with an electronic simulator, and the channel for the capnogram was calibrated with 5% carbon dioxide at the beginning of each study day.

An observer was present throughout each case to record intraoperative events. Hypercarbia was defined as an end-tidal carbon dioxide value ≥55 mm Hg for ≥60 s. In patients for whom P_{ECO_2} data were not available to the anesthesia team, the observer informed the team after 60 s of hypercarbia. An arrhythmia was defined as any impulse not generated by the sinus node, such as premature ventricular and atrial beats or ventricular bigeminal rhythm, which persisted for more than three beats; sinus tachycardia, sinus bradycardia, and nodal rhythms were not considered arrhythmias. An arrhythmia in the absence of hypercarbia that was associated with a strong stimulus (e.g., skin incision, traction of the spermatic cord) *and* signs of a shallow anesthetic level (e.g., patient movement, increase in heart rate or arterial blood pressure) that disappeared after anesthetic level deepened was attributed to light anesthesia. Because the measurement of P_{ECO_2} during anesthesia administered by a face mask is not as accurate as that during anesthesia administered through an endotracheal tube, the data from those two groups were analyzed separately.

Because of possible dependence between multiple arrhythmias in the same patient, all tests were performed on counts of *patients* rather than *events*. Fisher's exact test (two-sided) was used to evaluate the relationship between hypercarbia and arrhythmia and between the use of halothane and arrhythmia.

Table 1. Demographic Characteristics of Patients

	Airway management	
	Tracheal intubation	Face mask
No. of patients	196	206
Age (yr)	3.7 ± 4.4	5.1 ± 4.1[a]
Weight (kg)	17.7 ± 16.4	21.3 ± 13.6[a]
Duration of anesthesia (min)	96 ± 63	47 ± 20[a]

Values are mean ± SD.
[a] Significantly different versus intubated patients (P = 0.016–0.001).

Results

Four hundred two patients were studied. Children whose airways were managed via a face mask were older, weighed more, and had briefer surgical procedures compared with those managed with endotracheal intubation (P = 0.016–0.001) (Table 1). Overall, 21 of 206 patients whose airways were managed via a face mask (10.2%) experienced a persistent arrhythmia versus 3 of 196 patients (1.5%) whose airways were managed by endotracheal intubation (P = 0.0002). There were no arrhythmias observed in the 153 infants and toddlers younger than 2 yr, whereas 24 of 249 children 2 yr or older experienced 27 arrhythmic episodes (P = 0.0001) (Figure 1). Seventeen of the 24 episodes of arrhythmia in patients whose airways were managed via a face mask and two of the three episodes in the tracheally intubated patients occurred during maintenance of anesthesia. None of the arrhythmias required specific treatment or were associated with hemoglobin desaturation.

We focused our analysis on those children 2 yr or older as no children younger than 2 yr experienced an arrhythmia. Three of 90 children managed by endotracheal intubation experienced an arrhythmia; one was associated with hypercarbia, one with light anesthesia; and in the other, the cause was not clear.

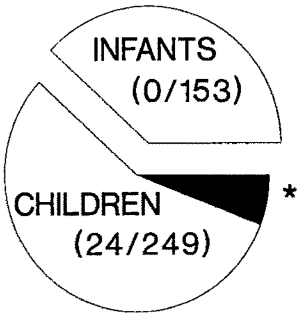

Figure 1. Age distribution of patients who experienced at least one episode of arrhythmia. Note that infants younger than 2 yr did not experience arrhythmia, whereas 24 children 2 yr or older did experience arrhythmia (*solid pie*). (*P = 0.0001).

Table 2. Incidence of Arrhythmias and Association With Hypercarbia and Light Anesthesia

	Airway management	
	Tracheal intubation	Face mask
No. of patients	90	159
Hypercarbia (no arrhythmia)	19	7
Hypercarbia with arrhythmia	1	9[a]
Light anesthesia with arrhythmia	1	8
No cause with arrhythmia	1	7
Total patients with arrhythmias	3	21[b]

[a] P = 0.0014. One patient experienced three arrhythmias (two with hypercarbia and one with light anesthesia). One other patient experienced two episodes of arrhythmia, both associated with hypercarbia.

[b] P = 0.01, mask versus tracheal intubation.

Table 3. Mean End-Tidal Carbon Dioxide Values in All Patients With Hypercarbia and Those With and Without Arrhythmias

	P_{ECO_2}			
	n	Mean	SE	Range
All patients	70	65.7	0.80	55–85
Hypercarbia only	60	65.7	0.85	56–85
Hypercarbia with arrhythmia	10	64.8	2.60	55–78

Values are in millimeters of mercury (mm Hg).

There were 19 episodes of hypercarbia not associated with arrhythmia in the tracheally intubated patients. Twenty-four episodes of persistent arrhythmias developed in 21 of 159 children whose airways were managed via a face mask. Sixteen of these patients experienced episodes of hypercarbia; nine episodes of arrhythmias in seven patients were associated with hypercarbia (P = 0.0014) (Table 2). Eight episodes in eight patients were associated with light anesthesia; and in seven patients with seven episodes, the cause was not clear (one patient experienced three separate episodes of arrhythmias, two associated with hypercarbia and one with light anesthesia; another patient experienced two episodes of arrhythmias associated with hypercarbia) (Table 2). The mean and range of P_{ECO_2} values for patients who had hypercarbia alone and those who had arrhythmias associated with hypercarbia were not significantly different (Table 3). The availability of capnography data did not influence the incidence of arrhythmias as four arrhythmia episodes associated with hypercarbia occurred in the group with capnography data available, whereas five occurred in the group without capnography data; likewise, the availability of pulse oximetry data did not affect the incidence of arrhythmias.

Although there was a strong relationship between hypercarbia and arrhythmias in the patients whose airways were managed via a face mask (9 of 16 episodes of hypercarbia), no such relationship was observed for patients managed by endotracheal intubation (1 of 20 episodes of hypercarbia). An equivalent proportion of arrhythmias were attributed to light anesthesia and to hypercarbia. We could not establish a statistical relationship between the occurrence of an arrhythmia and light anesthesia because there were no data for comparison as we did not record how many episodes of light anesthesia were not associated with an arrhythmia.

A total of 75 infants and toddlers younger than 2 yr had herniorrhaphy (57) or orchiopexy (18) operations with no persistent arrhythmias, whereas 85 children 2 yr or older had herniorrhaphy (62) or orchiopexy (23) operations with intraoperative arrhythmias developing in 14 patients. Twenty-four percent (13/55) of children undergoing these two procedures by face mask experienced at least one episode of arrhythmia compared with 3.3% (1/30) of children managed by endotracheal intubation (P = 0.016). These two surgical procedures were associated with 58% of the intraoperative arrhythmias despite accounting for only 34% of the surgical procedures.

Overall, 338 patients were anesthetized with halothane, whereas 64 patients were anesthetized with other techniques (34 with isoflurane; 20 with enflurane; and 10 with nitrous oxide, a narcotic, and a muscle relaxant). Examining only those patients 2 yr or older showed that 23 of 198 children anesthetized with halothane (11.6%) and 1 of 51 children anesthetized with other anesthetics (2.0%) had an arrhythmia (P = 0.035).

In 78 of the 196 patients whose tracheas were intubated, a Mapleson D nonrebreathing system was used; the remainder were managed with a pediatric circle system. The mean weight (± SD) of these 78 patients was 8.2 ± 4.6 kg. In 30 of these 78 patients, an endotracheal tube with a special tip-sampling line was used; and in 10 of these 30 patients, a simultaneous sample was also obtained from the right-angle connector. The mean difference (± SE) of the end-tidal carbon dioxide as sampled from the distal tip of the endotracheal tube and from the proximal connector in these 10 patients was 3.5 ± 0.6 mm Hg.

Discussion

The overall incidence of arrhythmias during routine pediatric anesthesia in our study (6.0%) is lower than that reported in patients under 30 yr (11.8%) (6). However, when we eliminate data from the 153 infants and toddlers younger than 2 yr who did not experience an arrhythmia, our incidence (9.6%) is similar to that in young adults. Our data support the concept that the frequency of anesthesia-associated arrhythmias is directly related to age (6).

A significantly larger incidence of ventricular arrhythmias occurred in children whose airways were managed via a face mask (13.2%) compared with those managed by endotracheal intubation (3.3%). We observed only one episode in 20 tracheally intubated patients with hypercarbia. The patient with the highest P_{ECO_2} value (85 mm Hg) was tracheally intubated and did not have an arrhythmia. In contrast, ventricular arrhythmias developed in 13% of children whose airways were managed via a face mask. There was a strong relationship between hypercarbia and ventricular arrhythmias in these patients ($P = 0.0014$).

The probable cause for the development of arrhythmias associated with hypercarbia is catecholamine release (6–11). The assumed pathophysiologic mechanism by which hypercarbia gives rise to cardiac arrhythmias is an increase in catecholamines in response to elevated blood carbon dioxide levels. However, the time-response and dose-response relationship between elevated Pa_{CO_2} levels and the occurrence of cardiac arrhythmias in adults or in children are not known. It is possible that a higher incidence of arrhythmias would have occurred had we allowed a less rigid control of the P_{ECO_2} range, i.e., if hypercarbia had been allowed to persist for longer than 60 s or if a higher value had been allowed before intervention.

When these data are interpreted superficially, endotracheal intubation appears to be the preferable airway management for prevention of ventricular arrhythmias in children. However, a variety of factors may have accounted for this striking difference between the tracheally intubated and the nonintubated patients. Perhaps the patients whose airways were managed via a face mask had inadequate depth of anesthesia compared with the tracheally intubated patients. A deeper anesthetic level may be maintained in tracheally intubated patients as required for smooth laryngoscopy and for suppression of bronchial responses owing to the endotracheal tube. In fact, eight episodes of arrhythmias during anesthesia managed via a face mask were actually attributed to light anesthesia by the attending anesthesiologist because of other patient responses (movement, increase in heart rate or arterial blood pressure); an equivalent proportion of arrhythmias in the patients managed by endotracheal intubation (1 of 3) was also attributed to light anesthesia.

Additionally, the majority of arrhythmias occurred during two types of surgical procedures (hernia and orchiopexy). This observation is consistent with the clinical difficulty in maintaining an adequate depth of anesthesia during procedures in which the level of surgical stimulation varies from moment to moment. Silver et al. (12) reported a similar experience (5 of 100 pediatric patients had arrhythmias); the patients who had ventricular arrhythmias were all undergoing repair of inguinal hernia or orchiopexy. Perhaps, catecholamine release in response to light anesthesia contributed in part to these arrhythmias (13).

The dose of exogenous or the level of endogenous catecholamines required to produce arrhythmias is lower with than without the use of halothane (1,11,14–16). A study comparing halothane, enflurane, and isoflurane in outpatient pediatric dental anesthesia reported a 14% incidence of ventricular arrhythmias when halothane was used as compared with no ventricular arrhythmias when enflurane and isoflurane were used (17). Increasing the halothane concentration does not decrease the carbon dioxide threshold to produce arrhythmias as is reported for cyclopropane (7,15). The myocardial "halothane sensitization" to catecholamines is apparently less marked in children; this observation may explain in part the lower incidence of arrhythmias in infants and toddlers younger than 2 yr who were anesthetized with halothane (18,19). The lower frequency of halothane-associated arrhythmias in infants and toddlers may also be due to electrophysiologic differences between the heart of the infant and that of the adult, i.e., infants have faster repolarization and shorter action potentials that might protect against reentry arrhythmias (20–22).

The comparably high frequency of arrhythmias in the children whose airways were managed via a face mask may therefore be explained by a combination of light anesthesia and detected and/or undetected hypercarbia, both leading to secondary release of catecholamines which, in combination with halothane, then gives rise to arrhythmias. Bearing in mind the difficulty in obtaining accurate P_{ECO_2} measurements in patients whose tracheas are not intubated, the actual Pa_{CO_2} in the seven patients managed by mask whose arrhythmias were neither associated with hypercarbia nor attributed to a light anesthetic level may actually have been higher than measured. The striking difference in the incidence of arrhythmias in the tracheally intubated compared with the nonintubated patients clearly suggests that endotracheal intubation has a salutory effect on the development of arrhythmias. Whether this is due to a better control of blood carbon dioxide values or to a deeper plane of anesthesia is purely speculative; however, as the proportion of ventricular arrhythmias attributed to light anesthesia was the same in both types of airway management, it is our interpretation that light anesthesia is at least one of the major contributory factors.

There is some controversy regarding the optimal sampling site for measurement of end-tidal carbon dioxide in tracheally intubated children using a nonrebreathing system (23). This issue is moot in this study because no persistent arrhythmias were observed in the patients who were anesthetized with the Mapleson D circuit configuration.

We conclude that the incidence of persistent perianesthetic cardiac arrhythmias in children without preexisting risk factors is approximately 10%, with no arrhythmias observed in infants younger than 2 yr. Although we observed a strong relation between hypercarbia and ventricular arrhythmias in children whose airways were managed via a face mask, other factors such as insufficient depth of anesthesia and the combined effect of halothane and hypercarbia are at least as important arrhythmogenic factors as hypercarbia alone. Persistent cardiac arrhythmias are commonly observed during anesthesia given via a face mask for repair of herniorrhaphy and orchiopexy; however, endotracheal intubation may reduce the incidence of arrhythmias through nonspecific mechanisms in these patients. The availability of P_{ECO_2} monitoring did not influence the incidence of arrhythmias associated with hypercarbia or the overall incidence of arrhythmias.

We thank Mark Marshall, Bioengineering technician, Charles Wickens, associate clinical engineer, and Richard DeCesare, clinical engineering manager, for their help with modifying and maintaining the monitoring equipment; all members of the pediatric anesthesia team, the anesthesia residents, and our pediatric surgeons for their help with the study; and Dr. Alan Zaslavsky, assistant professor of Statistics, Harvard University, for statistical analysis.

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Anesthetic Management of Infants Receiving an Adult Kidney Transplant

David S. Beebe, MD, Kumar G. Belani, MBBS, MS, Pam Mergens, MD, Ji-Chia Liao, MD, PhD, Samuel K. S. So, MD, John S. Najarian, MD, and Richard J. Palahniuk, MD

Departments of Anesthesiology and Surgery, University of Minnesota, Minneapolis, Minnesota

Renal transplantation in infants has been associated with a high incidence of acute tubular necrosis and of renal artery thrombosis. Since 1978, 24 infants who received an adult kidney transplant at the University of Minnesota have had aggressive administration of intravenous colloids to increase the central venous pressure to 16–20 mm Hg before renal reperfusion. Acute tubular necrosis developed in only two infants, and there were no cases of renal artery thrombosis. Chest radiographic evidence of pulmonary edema was present in the recovery room in seven patients (29%) and within the first four postoperative days in five patients (21%). Yet, only two infants (8.3%) required postoperative mechanical ventilation beyond 24 h to manage fluid overload. With aggressive intravenous colloid administration, infants in renal failure can receive an adult kidney transplant with a low incidence of active tubular necrosis or renal artery thrombosis, but pulmonary edema may develop requiring ventilatory support.

(Anesth Analg 1991;73:725–30)

Transplantation of an adult kidney into an infant who has renal failure is becoming more common. Previously formidable morbidity and mortality (1,2) have improved with better surgical technique, anesthetic management, preoperative blood transfusion, and the use of cyclosporine (3,4). The advantages of early renal transplantation are: (a) elimination of the need for maintenance dialysis, (b) improvement in renal osteodystrophy associated with dialysis, (c) improvement and acceleration of growth and development, (d) long-term graft and patient survival comparable to older children and adults (3,4).

Infants with renal failure present the following problems for anesthesia: (a) they are often malnourished and are small for their age; (b) they are kept relatively dehydrated by diet and dialysis; (c) they are anemic and often hyperkalemic and acidotic; (d) they may have uremic cardiomyopathy with stiff, noncompliant ventricles, cardiomegaly, and left ventricular hypertrophy (1,3–7).

The transplantation involves anastomosis of the adult kidney to the infant's aorta and inferior vena cava after cross-clamping both the aorta and inferior vena cava (8). On release of the aortic and inferior vena caval clamps, the ischemic lower extremities and new kidney are reperfused, which may cause acute hypovolemia and acidosis. The new kidney may sequester approximately 300 mL of blood and aggravate hypotension and may initially produce urine in amounts equal to the infant's blood volume every hour, further aggravating hypotension (4). This hypotension has been implicated in causing acute tubular necrosis (ATN) in the new kidney and may also precipitate renal artery thrombosis (2). Washout of the preservative solution from the kidney into the patient can cause life-threatening hyperkalemia and hypothermia (8,9). Finally, the infant's abdomen must accommodate a new, large organ which, in addition to receiving a large percentage of the cardiac output, may impede respiration and decrease venous return (8).

We reviewed the anesthetic and perioperative management of 24 infants younger than 1 yr who received an adult kidney at the University of Minnesota between January 1978 and March 1991. This retrospective analysis allows prediction of the hemodynamics, proper intravenous fluid management, and perioperative complications unique to this operation.

Methods

Twenty-four infants younger than 1 yr who received an adult kidney between January 1978 and March

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Accepted for publication July 29, 1991.

Address correspondence to Dr. Beebe, Department of Anesthesiology, University of Minnesota, B515 Mayo, Box 294, 420 Delaware Street, Minneapolis, MN 55455.

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0003-2999/91/$3.50

1991 were reviewed retrospectively. Anesthesia was induced and maintained in a variety of ways. All patients had central venous pressure (CVP) monitoring established through a Hickman dialysis catheter placed before induction of anesthesia or after. One patient had the CVP monitored through a percutaneous cervical intravenous line. Twenty-three patients had radial arterial catheters inserted after induction of anesthesia and routine monitoring.

The surgical technique has been described in detail previously (8). Briefly, an anastomosis of the adult renal artery and vein to the clamped infant aorta and inferior vena cava was performed after reflecting the ascending colon. Reperfusion of the donor kidney followed unclamping of these vessels after completion of the anastomoses. The ureter was then implanted into the bladder.

Intraoperatively, packed red blood cells, fresh frozen plasma, hetastarch, or 5% albumin were given intravenously along with maintenance crystalloids to achieve a CVP of 16–20 mm Hg before the release of the aortic and caval cross-clamps. Mannitol (0.5–1.0 g/kg) and furosemide (1 mg/kg) were also administered intravenously before the release of the cross-clamps to ensure a brisk diuresis. Sodium bicarbonate (1 mEq/kg) was also given intravenously to counteract the acidosis from the ischemic lower extremities and renal allograft. At the time of unclamping, the kidney was externally warmed with saline lavage to counteract the hypothermic effect of the cold perfusate washed out of the kidney. If necessary, fluids were given intravenously after the cross-clamps were released to correct hypotension. Calcium chloride (10 mg/kg) and/or dopamine were used in some cases. After renal perfusion, additional sodium bicarbonate (1 mEq/kg) was given if the pHa remained less than 7.30 despite adequate ventilation ($Paco_2$ between 30 and 40 mm Hg). Calcium chloride or potassium chloride was administered as needed based on laboratory values.

Urine output after renal reperfusion was measured every 15 min and was replaced with a standard crystalloid containing glucose (5 mg/dL), sodium chloride (0.45 mEq/L), sodium bicarbonate (10 mEq/L), and potassium supplementation as required. This regimen was continued for 2 days postoperatively to ensure adequate hydration in the early posttransplantation period when a brisk diuresis may occur. Changes in glucose and electrolytes content was made on the basis of serum and urinary electrolytes and blood sugar concentrations. Furosemide was given intravenously for oliguria in the presence of an adequate CVP. Colloids consisting of packed red blood cells, fresh frozen plasma, and 5% albumin were administered as needed, guided by the CVP, arterial blood pressure, heart rate, hematocrit, coagulation status, and chest radiograph appearance.

Chest radiographs were obtained immediately after operation in all patients and frequently during the first week depending on clinical condition. Their tracheas were extubated when muscle power returned to normal, arterial blood gases were adequate, and chest radiographs appeared clear.

The intraoperative colloid volume expansion was defined as

$$\frac{\text{Volume of blood products and colloids given} - \text{Blood loss}}{\text{Body weight}}$$

and was correlated with the postoperative chest radiograph appearance.

Intraoperative temperature, CVP, arterial blood pressure, and heart rate were recorded for each patient: (a) at the beginning of the operation, (b) immediately after cross-clamping the aorta and vena cava, (c) 5 min after cross-clamp release, (d) at the end of the operation, and (e) on arrival in the recovery room. Analysis of arterial blood gases, glucose, and electrolytes was recorded before cross-clamping, after release, and in the recovery room. Daily urine output and serum creatinine levels were recorded for 1 wk after operation. A radionucleotide renogram was obtained postoperatively if ureteral obstruction, ATN, or vascular occlusion was suspected.

Results were recorded as mean ± SD. Paired *t*-tests were used to compare hemodynamics and laboratory values before and after renal reperfusion. Analysis of variance and unpaired Student's *t*-tests were used to compare hemodynamics and intravenous fluid administration between patients in whom pulmonary edema or ATN developed or did not develop. Significance was defined as $P < 0.05$.

Results

Fourteen male and 10 female infants received adult kidney transplants between 1978 and 1991. Nine patients received kidney transplants from 1978 through 1984, and 15 patients received transplants from 1985 until the present time. The age at transplant (±SD) was 9.4 ± 2.0 mo (range, 6–12 mo). The average body weight was 6.7 ± 0.8 kg (range, 4.8–7.7 kg). Renal failure was caused by renal dysplasia or obstructive uropathy in 15 patients. Of the remaining nine, four had oxalosis, two had congenital nephrotic syndrome, one had proliferative glomerulonephritis, one had renal loss caused by ATN after orchidopexy surgery, and one had renal failure from an unknown cause.

Eight patients had cardiomegaly preoperatively, but none had congenital heart disease. Nineteen patients were receiving dialysis (8 hemodialysis, 11

Table 1. Blood Loss and Volume Replacement

	EBL	Crystalloid	FFP	5% Alb	Hetastarch	PRBC	WB
n	24	24	19	15	1	23	1
Absolute volume (mL)	220 ± 180	383 ± 243	336 ± 240	336 ± 240	100	334 ± 150	355
Volume/body weight (mL/kg)	33.7 ± 28.7	52.1 ± 33.3	52.8 ± 41.1	47.3 ± 35.5	13.0	50.9 ± 25	41

EBL, estimated blood loss; FFP, fresh frozen plasma; Alb, albumin; PRBC, packed red blood cells; WB, whole blood; *n*, number of patients receiving components.

Values are mean ± SD.

Table 2. Hemodynamic Data

	Preinduction	30 Min after induction	5 Min before (X)	Mid (X)	5 Min before Un (X)	5 Min after Un (X)	End of operation	PAR	24 Hours after operation
SBP (mm Hg)	95 ± 19	96 ± 20	107 ± 3[a]	111 ± 19[a]	121 ± 28[a]	99 ± 14[b]	114 ± 29[a]	116 ± 19[a]	109 ± 19[a,c]
HR	122 ± 19	145 ± 20	133 ± 17	132 ± 17[a]	137 ± 24	146 ± 26[b]	146 ± 20	161 ± 23[a]	139 ± 23[c]
CVP (mm Hg)	NM	6.6 ± 3.0	10.8 ± 3.2[a]	14.0 ± 4.2[a]	16.2 ± 4.6[a]	10.5 ± 4.5[a,b]	10.2 ± 3.0[a]	7.5 ± 4.0	7.9 ± 4.2
Esophageal temperature (°C)	NM	36.4 ± 0.5	36.7 ± 0.7	36.7 ± 0.7	36.6 ± 0.7	36.4 ± 0.8	37.0 ± 0.9[a]	NA	NA

Ind, induction; (X), cross-clamp of aorta and vena cava; Un (X), unclamping; PAR, recovery room; SBP, systolic blood pressure, HR, heart rate; CVP, central venous pressure; NM, not measured; NA, not available.

Values are mean ± SD.

[a] $P < 0.05$ compared with data 30 min after induction.

[b] $P < 0.05$ compared with data 5 min before unclamping of aorta and vena cava.

[c] $P < 0.05$ compared with data before induction of anesthesia.

peritoneal dialysis) at the time of transplantation. Nineteen patients received kidneys from a parent, three from an adult relative other than a parent, one from a nonrelated friend of the patient's family, and one from an adult cadaver. Silica gel-fractionated plasma was used as the renal preservative solution in all cases.

Anesthesia was induced with halothane in 7 patients, with intravenous ketamine in 7 patients, and with intravenous thiopental in 10 patients. Anesthesia was maintained with isoflurane in 20 patients and with halothane in 4. Paralysis was achieved with pancuronium in 6 patients, vecuronium in 5 patients, atracurium in 10 patients, and *d*-tubocurarine in 3 patients. All nine patients who received either pancuronium or *d*-tubocurarine received their kidney transplants before 1985. Five patients received succinylcholine to facilitate tracheal intubation.

The average duration of the operation and anesthesia was 6.5 ± 0.9 h. Table 1 lists the volume of blood loss and the amount of blood, colloid, and crystalloid administered during the operation. The average intraoperative intravenous colloid administration was 90 ± 41 mL/kg.

As seen in Table 2 and Figure 1, there was a decrease in arterial blood pressure and CVP and an increase in heart rate with reperfusion of the kidney. Esophageal temperature did not decline significantly with organ reperfusion.

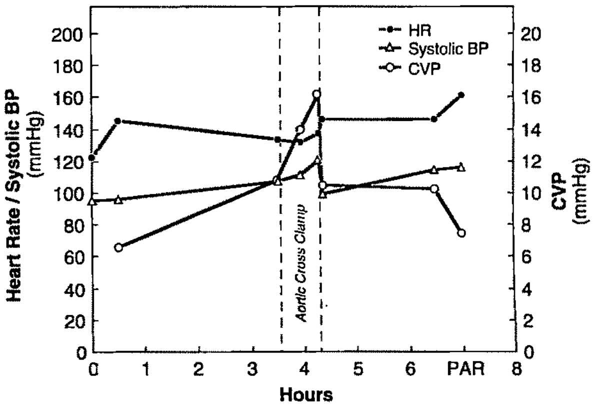

Figure 1. Mean systolic blood pressure (BP), central venous pressure (CVP), and heart rate versus time.

Table 3 lists the acid base data. At the start of the operation, all patients had mild metabolic acidosis. With the administration of sodium bicarbonate before renal reperfusion, the acidosis resolved and remained corrected throughout the operation.

Table 4 lists the electrolyte values both intraoperatively and postoperatively. The average potassium level after cross-clamp release was 3.8 ± 1.0 mmol/L (range, 2.1–6.0 mmol/L), not different from before cross-clamp release (4.0 ± 1.0 mmol/L, $P > 0.05$).

Table 3. Acid Base Data

	After induction	Before (X)	After Un (X)	End of operation	PAR	24 Hours after operation
n	22	22	22	17	23	19
pHa	7.38 ± 0.09	7.36 ± 0.05	7.32 ± 0.10	7.39 ± 0.09	7.41 ± 0.07	7.41 ± 0.04
Pa_{CO_2} (mm Hg)	33.0 ± 10.2	33.3 ± 7.4	38.9 ± 6.6^a	37.1 ± 6.9	37.8 ± 6.0	35.1 ± 6.6
Pa_{O_2} (mm Hg)	168 ± 79	173 ± 76	180 ± 83	186 ± 98	158 ± 63	114 ± 51^b
HCO_3 (mEq/L)	19.5 ± 4.9	18.9 ± 3.8	19.8 ± 3.0	21.5 ± 2.9	22.9 ± 3.6^b	21.8 ± 2.9^b
F_{IO_2}	0.55 ± 0.18	0.51 ± 0.16	0.53 ± 0.18	0.52 ± 0.19	0.45 ± 0.08^b	0.31 ± 0.08^b

(X), cross-clamp of aorta and vena cava, Un (X), unclamping; PAR, recovery room; *n*, number of patients with data; F_{IO_2}, inspired oxygen fraction.
^{a}$P < 0.05$ compared with data before cross-clamp of aorta and vena cava.
^{b}$P < 0.05$ compared with data after induction of anesthesia.

Table 4. Electrolytes, Glucose, and Hemoglobin

	Preop	After induction	Before (X)	After UN (X)	PAR	24 Hours after operation	7 Days after operation
n	24	21	17	20	24	24	24
Sodium (mmol/L)	139.8 ± 7.0	135.5 ± 8.4	136.4 ± 7.1	138.5 ± 5.1	140.6 ± 4.6^a	140.0 ± 5.7^a	135.9 ± 3.0
Potassium (mmol/L)	4.1 ± 0.6	4.0 ± 0.9	4.0 ± 1.0	3.8 ± 1.0	3.4 ± 0.6^a	3.8 ± 0.6	4.3 ± 0.7
Calcium (mg/dL)	9.6 ± 1.0 (9)	7.9 ± 0.7 (6)^a	NA	NA	8.4 ± 1.2 (7)^a	8.4 ± 0.9 (21)^a	8.6 ± 0.8^a
Chromium (mg/dL)	3.64 ± 1.38	NA	NA	NA	2.07 ± 0.91 (20)^a	0.76 ± 1.17 (23)^a	0.49 ± 0.45^a
Glucose (mg/dL)	92 ± 15	NA	NA	NA	280 ± 123 (22)^a	115 ± 42 (23)^a	125 ± 68 (22)^a
Hemoglobin (g/dL)	9.8 ± 2.0	NA	NA	NA	12.7 ± 3.7	11.4 ± 2.1 (23)^a	9.1 ± 1.6 (23)

n, number of patients with data; (X), cross-clamp of aorta and vena cava; PAR, recovery room; NA, not available.
Values are mean ± SD.
Numbers within parentheses give numbers of patients reported if less than *n*.
^{a}$P < 0.05$ compared with values measured before patient's operation.

Nineteen patients (79%) had immediate function of their allografts that continued through 1 wk postoperatively. Five patients (24%), however, had graft dysfunction in the first postoperative week. One patient lost the allograft after a twist developed in the renal vein postoperatively. One patient had a reaction to antilymphocyte globulin, administered as part of the antirejection protocol, resulting in loss of approximately 40% of the allograft function. One patient had diminished renal function on postoperative day 3, which was thought to be caused by dehydration that responded to intravenous fluid administration. Two patients had minimal initial urine outputs, elevated serum creatinine levels, and ATN by renogram. Both recovered and had good renal function by the first postoperative week, although one required dialysis on postoperative day 2.

In the two patients in whom ATN developed, there was no difference in the intraoperative colloid volume expansion (104 ± 39 mL/kg vs 89 ± 42 mL/kg, $P > 0.05$), in the pregraft reperfusion systolic blood pressure (114 ± 2 mm Hg vs 121 ± 29 mm Hg, $P > 0.05$), or in the CVP pregraft reperfusion (11.0 ± 4.2 mm Hg vs 16.6 ± 4.4 mm Hg, $P > 0.05$) from that of infants in whom ATN did not develop. There was also no significant difference in the post-unclamping systolic blood pressure (80 ± 14 mm Hg vs 101 ± 14 mm Hg, $P > 0.05$), in heart rate (126 ± 28 vs 148 ± 26 beats/min, $P > 0.05$), or in CVP (8.0 ± 1.4 mm Hg vs 10.7 ± 4.6 mm Hg, $P > 0.05$) in the ATN group compared with that of the other patients. However one of the patients in whom ATN developed required resuturing of the arterial and venous limbs of the allograft because of technical problems with the first anastomosis. The allograft received therefore a longer warm ischemia time compared with the other kidneys.

In both cases, the ATN resolved by postoperative day 7, and both patients were discharged with functioning allografts. One allograft that had ATN is currently functioning 53 mo after transplantation, and the second functioned until the patient's death 69 mo after transplantation.

The mean duration of tracheal intubation from the onset of operation was 20 ± 25 h (range, 4.75–103 h) with the tracheas of 17 patients extubated in the recovery room and that of 4 patients on the following day. The tracheas of two patients were intubated for 76 and 58 h to help manage excessive intravenous fluids and atelectasis. The patient who lost his graft because of a twist in the renal vein had endotracheal intubation for 103 h owing to his requiring multiple operations during this time.

Chest radiographic evidence of pulmonary edema developed in seven patients in the recovery room. In addition, chest radiographic evidence of pulmonary edema developed in five patients during the first four postoperative days. There was no significant difference in the amount of intraoperative colloid administered between the infants with chest radiographic evidence of pulmonary edema either in the recovery room (75 ± 47 mL/kg) or within the first four postoperative days (113 ± 32 mL/kg) and those in whom chest radiographic evidence of pulmonary edema did not develop (90 ± 41 mL/kg, $P > 0.05$). The CVP was also not significantly different 5 min before graft reperfusion in those patients in whom pulmonary edema developed in the recovery room (15.3 ± 4.6 mm Hg) or during the first four postoperative days (14.2 ± 4.8 mm Hg) compared with those without pulmonary edema (17.5 ± 4.4 mm Hg, $P > 0.05$), nor was the CVP significantly different between the three groups after cross-clamp release (8.8 ± 3.7, 9.8 ± 4.2, 11.7 ± 4.9 mm Hg, $P > 0.05$) or in the recovery room (7.6 ± 2.8, 10.8 ± 6.2, 9.1 ± 2.7 mm Hg, $P > 0.05$). There also was no difference in the calculated alveolar-arterial oxygen gradients measured in the recovery room between the patients with chest radiographic evidence of pulmonary edema in the recovery room (120 ± 79 mm Hg) or in the first four postoperative days (140 ± 93 mm Hg) and those without radiographic evidence of pulmonary edema (101 ± 62 mm Hg). The chest radiographic changes all resolved by postoperative day 7.

Atelectasis was the other common chest radiographic finding postoperatively, occurring as an isolated finding in 10 patients and associated with pulmonary edema in six. Chest physiotherapy, diuresis, and positive pressure ventilation were the prime modes of therapy, but one patient required bronchoscopy to expand a right upper lobe atelectasis.

Since 1978, three of the patients in the series have died (12.5%). Two patients died of overwhelming pneumococcal sepsis 50 and 70 mo after transplantation. Both patients had received pretransplantation splenectomies for immunosuppression. The other patient died of recurrent oxalosis and cerebral edema 14 mo after transplantation.

Three patients have lost their allografts but are still living. One patient who received a cadaver transplant lost the allograft at 88 mo owing to chronic rejection. Two other patients lost their grafts at 23 and 14 mo because of recurrent oxalosis.

Currently, 17 of the 24 patients in the series (71%) have functioning renal transplants (the longest functioning for 107 mo) and are not requiring dialysis.

Discussion

Early experience with kidney transplantation in infants and small children was complicated by a high incidence of renal artery thrombosis and ATN. Inadequate intravenous fluid administration was thought to contribute to these complications (2). Acute tubular necrosis developed in only two of our infants, and there were no incidents of renal artery thrombosis. All 24 infants in the series were transfused with blood products and colloids to a CVP between 16 and 20 mm Hg before cross-clamp release and received 90 ± 41 mL/kg of blood products or colloids in excess of blood loss during the operation.

Acute tubular necrosis developed in two children despite this regimen. Acute tubular necrosis may have developed in one of the children because of surgical difficulties requiring the vascular anastomosis to be resutured and thus prolonging the warm ischemia time of the renal allograft. There was, however, no significant difference in the hemodynamics between the patients in whom ATN developed and those in whom ATN did not develop, nor were there significant differences in the amounts of colloids or blood products given during operation.

Only one patient in whom ATN developed required dialysis. In both cases, the ATN resolved and the allografts exhibited no lasting impairment of renal function. This is consistent with the finding in older children and in adult kidney transplant recipients that allografts that recover from perioperative ATN do not have a poorer survival (10).

Chest radiographic evidence of pulmonary edema was a common complication, but it resolved early in most patients and was not associated with hypoxia. The CVP was not helpful in predicting this complication, nor was pulmonary edema directly correlated with the fluids administered intraoperatively. Rapid intravenous fluid administration required in the operation may acutely increase the pulmonary artery pressures in children with renal failure who may have a noncompliant left ventricle (5). This may precipitate pulmonary edema but may not be reflected by the CVP.

Atelectasis was the other common radiographic finding. Major abdominal surgery causes a postoperative diminution in the functional residual capacity in all patients and can predispose to atelectasis (11). The addition of a large adult kidney worsens this situation. With the presence of significant atelectasis or pulmonary edema on the postoperative chest radiograph, the patient should be mechanically ventilated until clearing of excessive fluid and reexpansion of collapsed areas occur.

Severe hyperkalemia, acidosis, and hypothermia after renal reperfusion were not seen in these patients. Hyperkalemia after renal reperfusion causing cardiac arrest has been associated with the use of solutions with high potassium concentrations, such as Collin's solution, for renal preservation (9). The use of silica gel-fractionated plasma in these 24 infants as renal preservative may have prevented a significant increase in serum potassium concentrations. Similarly, significant hypothermia was prevented by externally warming the kidney immediately before reperfusion. The mild metabolic acidosis present in most infants resolved with establishing function of the new kidney and correction by administration of sodium bicarbonate.

The main cause of death in infants who have received an adult kidney in this series was overwhelming pneumococcal septicemia that occurred in two patients. Both patients had splenectomies before transplantation. The increased risk of pneumococcal septicemia after splenectomy and the finding that pretransplant splenectomies did not increase allograft survival led our transplantation surgeons to abandon routine pretransplantation splenectomies in 1983 (3), and no infant who received a transplant after 1983 has had pneumococcal septicemia.

In summary, with aggressive perioperative colloid administration, infants in renal failure can receive an adult kidney transplant with prompt onset of renal function in most cases. Pulmonary edema is a common postoperative complication but is usually transient and resolves with diuresis from the new kidney. Atelectasis is also common and may require postoperative mechanical ventilation. Long-term results have been gratifying, however, and should continue to improve as the fields of immunology and transplantation advance.

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Plasma Inorganic Fluoride Concentrations During and After Prolonged (>24 h) Isoflurane Sedation: Effect on Renal Function

Elizabeth M. Spencer, BM, FCAnaes, Sheila M. Willatts, FRCP, FCAnaes, and
Cedric Prys-Roberts, DM, PhD, FCAnaes, FFARACS

Intensive Therapy Unit and Sir Humphry Davy Department of Anaesthesia, University of Bristol, Bristol Royal Infirmary, Bristol, United Kingdom

We studied the effect of prolonged sedation (>24 h) with isoflurane on plasma inorganic fluoride concentrations and renal function in 60 critically ill patients allocated randomly to receive either isoflurane or midazolam for sedation. In the isoflurane group, plasma fluoride increased from a mean concentration of 3.1 μmol/L to 20.0 μmol/L at the end of sedation, continued to increase to a peak of 25.3 μmol/L 16 h later, and then decreased exponentially ($t_{1/2}$ = 111 h) to reach normal levels by the fifth day. In the midazolam group, the plasma fluoride increased from a mean concentration of 4.2 μmol/L to a peak of 6.8 μmol/L 12 h after starting the sedation and then decreased toward normal. Serum and urinary electrolytes, urine osmolality, and creatinine clearance during and after sedation were similar in the two groups. Isoflurane sedation was associated with an increase in plasma fluoride concentration without any clinical deterioration of renal function.

(Anesth Analg 1991;73:731–7)

Most patients requiring controlled ventilation in the intensive therapy unit (ITU) need sedation to allay anxiety, to facilitate controlled ventilation, and to minimize the distress caused by unpleasant procedures. Many different drugs are currently used for this purpose, but all have disadvantages and side effects when given continuously to critically ill patients. Subanesthetic concentrations of isoflurane can produce satisfactory sedation during controlled ventilation with a rapid recovery (1).

Isoflurane undergoes partial metabolic biodegradation releasing inorganic fluoride ions. In 1973 Cousins and Mazze (2) showed that methoxyflurane-induced serum inorganic fluoride (F^-) concentrations of larger than 50 μmol/L were associated with a reduction in the kidney's ability to concentrate urine. Our previous work demonstrated that F^- concentration increased from 4.3 to 10 μmol/L after 18 h of isoflurane sedation without any deterioration of renal function (3).

If isoflurane is to be administered safely to sedate patients whose ventilation is mechanically controlled, the resultant F^- concentrations and their potential nephrotoxic level need to be determined. This study was subsequently designed to investigate the effect of isoflurane sedation for longer than 24 h on plasma inorganic fluoride concentrations and renal function in critically ill patients.

Methods

We studied 60 patients, aged 16–80 yr, admitted to the ITU who required ventilation for longer than 24 h. Patients were excluded if they had any evidence of intracerebral pathology (including potential cerebral hypoxic damage after cardiac arrest), severe liver or renal dysfunction, gross obesity, or pregnancy. The study was approved by the local District Health Authority Ethics Committee. Written informed consent was obtained from the patient or from the closest relative. The severity of illness in each patient was assessed on admission to the ITU using the APACHE II score. Ventilation was adjusted to try and maintain an arterial carbon dioxide tension between 30 and 40 mm Hg and an arterial oxygen tension of

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Supported by Abbott Laboratories, Maidenhead, United Kingdom.

Presented in part at the Anaesthetic Research Society Meeting, Nottingham, United Kingdom, July 1990.

Accepted for publication July 17, 1991.

Address correspondence to Dr. Spencer, Department of Anaesthesia, Derriford Hospital, Derriford Road, Plymouth PL6 8DH, United Kingdom.

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0003-2999/91/$3.50

100 mm Hg. Concurrent therapy such as intravenous fluids, blood transfusion, antibiotics, inotropic agents, and diuretics were administered as required, and standard supportive care was provided. The electrocardiogram, direct arterial blood pressure, and central venous pressure were routinely monitored. Patients were allocated randomly to receive either 0.1%–0.6% isoflurane in an air-oxygen mixture or a continuous intravenous infusion of 0.01–0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ of midazolam for sedation. In those patients who received isoflurane, end-tidal concentrations were measured with a Siemens Gas Monitor and MAC hours of isoflurane were calculated (4).

Sedation was started when the patient became restless after ITU admission. Using a modified Ramsay scale, the sedation level was assessed by the nursing staff every hour, and the dose of the sedative drug was increased or decreased as appropriate to maintain a desired level of sedation (1). Incremental intravenous doses of morphine (0.05 mg/kg) were given for analgesia as required. The trial drug was stopped when the patient was judged ready for weaning from ventilatory support (1).

The plasma concentrations of inorganic fluoride were measured in all patients before sedation, every 12 h during sedation, at the end of sedation, every 4 h for the first 24 h after sedation, and then daily for 6 days. In the midazolam group, samples were also taken after 4 and 8 h of sedation. Plasma samples were prepared by withdrawing 5.0 mL of arterial blood from each patient, transferring to fluoride-free lithium-heparin tubes, and mixing by inversion for 1 min before centrifuging at 700*g* for 15 min. Supernatant plasma was withdrawn and stored at −25°C. Care was taken to avoid fluoride contamination, particularly from glassware; and polypropylene flasks, vials, and micropipettes were used. Subsequently, ionic F^- concentrations were determined by using an ion-selective electrode (5–7). A combination pH electrode and a single F^- electrode were used together as a differential cell, potentials generated being measured with an Orion model 901 microprocessor (Orion Research, Cambridge, Mass.) incorporating two high-impedance inputs. To calibrate the cell, a range of sodium fluoride solutions were added to an acidic solution to provide calibration samples at the same acid strength (pH 1.2) and with a similar range of F^- concentrations as the samples to be tested. For each measurement, 0.2 mL of plasma was added to 0.6 mL of 0.1 M HCl and the mean of two successive measurements was recorded. Interassay coefficients of variation were 2.2% and 1.3% at mean plasma F^- concentrations of 2.0 and 30 μmol/L, respectively. The lower limit for fluoride determination was 0.1 μmol/L with linearity from the lower limit of detection to 90 μmol/L (correlation coefficient, $r = 0.999$).

Table 1. Details of Patients Studied

	Isoflurane group	Midazolam group
n	30	30
Sex (M/F)	19/11	21/9
Surgical/medical	20/10	24/6
Median age (range) (yr)	62 (17–80)	68 (32–77)
Mean weight (SD) (kg)	68 (10)	72 (14)
Median APACHE II score (range)	12 (1–23)	12 (3–24)
Median duration of sedation (range) (h)	36 (10–127)	36 (4–104)

To assess renal function, plasma and urinary electrolytes and creatinine were measured on admission to the ITU, daily during the period of sedation, when the sedation was stopped, and at 24 and 48 h later. Hourly urine output was recorded, and urine osmolality was measured regularly at the bedside using the Advanced Micro-Osmometer (model 3MO), which determines osmolality by means of freezing point depression.

Most of the biochemical data had a skewed distribution and so a logarithmic (base *e*) transformation was applied before analysis. Paired and unpaired *t*-tests were performed, using a pooled standard deviation, to compare means within and between groups, respectively. Adjustments for confounding factors were made using analysis of covariance.

Results

Table 1 shows details of the patients studied. The two groups of patients were comparable in sex distribution, weight, admission APACHE II score, and duration of sedation. The patients in the isoflurane group were slightly younger ($P = 0.03$). Twenty patients sedated with isoflurane and 24 of those sedated with midazolam had received a volatile anesthetic agent during operation before their admission to the ITU. Four patients in the isoflurane group and two in the midazolam group had received enflurane during operation, the remainder had received isoflurane.

On admission to the ITU, there was one particularly high plasma fluoride concentration observed in each group. These were found in patients who had received enflurane during operation, and so all the fluoride results of patients who had received enflurane were omitted from the analysis. On ITU admission, the mean (95% confidence interval) plasma fluoride concentrations in the two groups were 3.12 (2.49, 3.75) μmol/L in the isoflurane group and 4.25

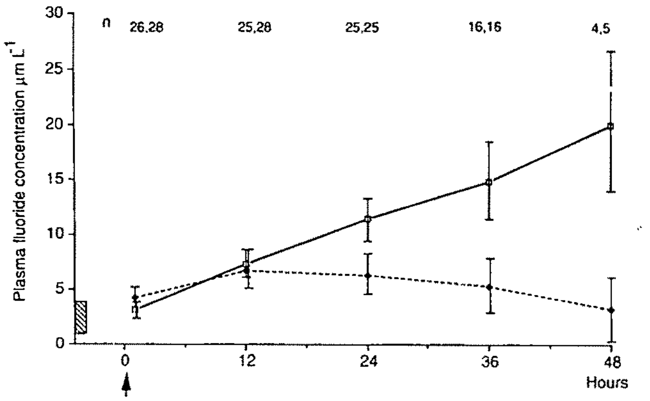

Figure 1. Mean plasma fluoride concentrations (95% confidence interval) before and during the period of sedation (in hours) showing the number of patients in the isoflurane and midazolam groups, respectively (*n*), at each time. The *shaded area* represents the range of normal values. -□-, Isoflurane group; ···◆···, midazolam group.

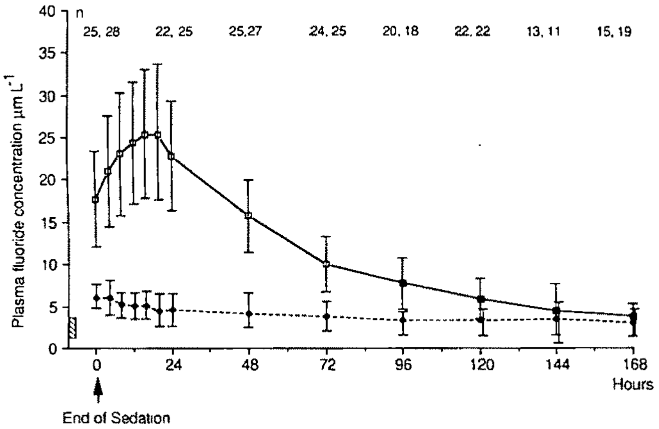

Figure 2. Mean plasma fluoride concentrations (95% confidence interval) after the period of sedation (in hours) showing the number of patients in the isoflurane and midazolam groups, respectively (*n*), at each time. The *shaded area* represents the range of normal values. -□-, Isoflurane group; ···◆···, midazolam group.

(3.41, 5.08) μmol/L in the midazolam group. In the isoflurane group there was a gradual increase in plasma F^- during the period of sedation to 20.01 (13.30, 26.73) μmol/L. In the midazolam group, the mean plasma F^- increased slightly to reach a peak of 6.76 (5.09, 8.44) μmol/L after 12 h of sedation and then returned to normal (Figure 1). After stopping the sedation, the mean plasma F^- in the isoflurane group continued to increase and reached a peak of 25.34 (17.69, 33.00) μmol/L 16 h after discontinuing the isoflurane (Figure 2). The plasma F^- at the end of sedation, the maximum plasma F^-, the difference between these two values, the time to reach the maximum F^-, and the rate of F^- rise did not correlate with the weight of the patient, using multiple regression. There was also no correlation found between plasma fluoride concentration and APACHE II score.

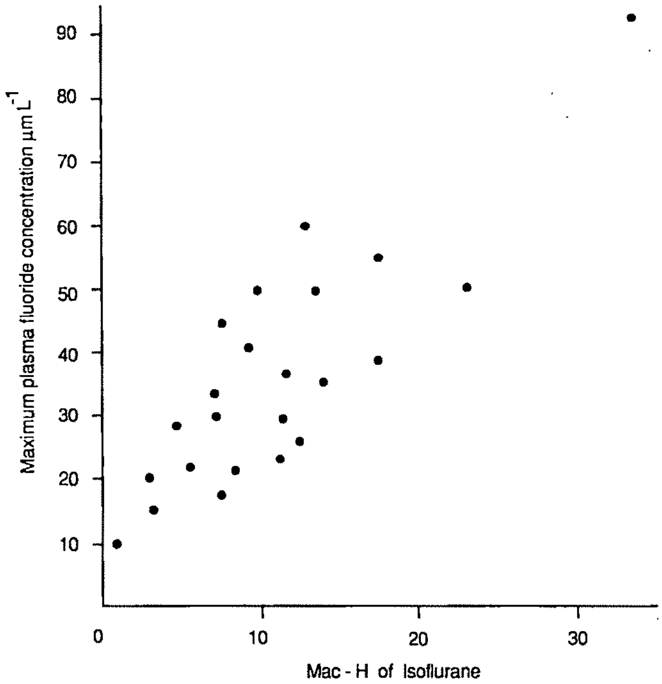

Figure 3. Relationship between the maximum plasma fluoride concentration and the MAC-hours of isoflurane. $n = 30$. $P < 0.001$, $R^2 = 54.9\%$.

Having reached a peak, the plasma F^- then followed a single exponential decay to reach normal concentrations by the fifth day (Figure 2). Using the last eight points on the graph, the half-life for inorganic fluoride in these patients was calculated to be 111.5 h, 95% confidence interval (98.41, 128.60).

There was a significant linear regression ($P < 0.001$, $R^2 = 54.9\%$) between the maximum plasma F^- in each patient in the isoflurane group and the MAC-hours of isoflurane that patient had received (Figure 3). The one outlying point was for one patient requiring a very long period of sedation, and this contributed significantly to the regression. Even if this point was ignored, the mean (95% confidence interval) dose of isoflurane used for sedation was 8.67 (7.17, 10.17) MAC-hours, and there was still a significant linear relationship between dose of isoflurane and plasma fluoride concentration ($P = 0.022$, $R^2 = 18\%$). There was no significant correlation between the plasma fluoride concentration and the serum creatinine concentration or any other measure of renal function.

There were no significant differences in serum and urinary electrolytes, creatinine clearance, or urine osmolality between the two groups either during or after sedation. For those patients who required 48 h of sedation, their measurements of renal function

Table 2. Plasma Creatinine and Urine Osmolality, Median (range), and Percent Change From Baseline for Those Patients Requiring a Longer Period (>48 h) of Sedation in the Two Groups Both During and After Sedation

	Creatinine (mg/dL)		Osmolality (mOsm/L)	
	Iso (n = 16)	Mid (n = 18)	Iso (n = 15)	Mid (n = 16)
During sedation				
Baseline	139 (62–448)	100 (59–155)	373 (310–1009)	381 (210–684)
24 h	153 (72–492)	116 (52–281)	424 (327–989)	458 (325–654)
Percent change	↑ 9	↑ 26	↑ 11	↑ 20
48 h	144 (53–544)	105 (51–391)	425 (293–708)	434 (285–742)
Percent change	↑ 12	↑ 21	↑ 6	↑ 24
After sedation				
End of sedation	144 (58–544)	101 (51–455)	433 (293–708)	503 (333–742)
Percent change	↑ 11	↑ 20	↑ 11	↑ 32
Day 1	145 (54–583)	88 (43–524)	487 (343–1028)	528 (292–732)
Percent change	↑ 3	↑ 12	↑ 24	↑ 34
Day 2	120 (53–622)	87 (51–617)	511 (348–855)	547 (305–784)
Percent change	↓ 9	↑ 9	↑ 25	↑ 34

Iso, = isoflurane; Mid, midazolam.

were analyzed separately. There were missing data for several patients because of demands of clinical care. The most common incomplete test was the 24-h urine collection, and thus not all urinary creatinine and creatinine clearance tests for those patients requiring longer sedation were available. Therefore, plasma creatinine and urinary osmolality were chosen for more detailed analysis. There was a significant difference in plasma creatinine at baseline between the two subgroups (P = 0.008) (Table 2). However, when percent change from baseline was calculated, there was no significant difference between the subgroups (Table 2).

The results of most of the biochemical tests had a skewed distribution, but the urine osmolality for both subgroups had a bimodal distribution suggesting two different patient samples. The urine osmolality was related to diuretic administration: the use of a diuretic decreased the osmolality. Having adjusted for the effect of diuretic, there was no difference between the two treatment groups in the urine osmolality at baseline or the percent change from baseline at any of the times analyzed. A χ^2-test was carried out for the number of patients in each treatment group who received diuretics at baseline and at daily intervals during and after sedation. There was no significant difference in the number of patients requiring diuretics in each of the groups at any of the times tested.

There were three patients in the isoflurane group and one patient in the midazolam group who required renal support in the form of hemodiafiltration.

Discussion

The results of a previous study looking at the effect of isoflurane sedation (i.e., <18 h) in critically ill patients in the ITU showed that the plasma level of inorganic fluoride increased more than would have been expected for the MAC-hours of isoflurane received (3). Our study looking at more prolonged isoflurane sedation confirms these findings. However, the increased serum fluoride concentration observed was not associated with any significant alteration in renal function.

Studies in humans have shown that after exposure to 3.1 MAC-hours of isoflurane during surgical procedures lasting 2–7.5 h, serum F^- increased to mean values of 4.4 μmol/L from preoperative baseline values of 2.2 μmol/L (14). Up to 6.5 MAC-hours of isoflurane anesthesia produced a maximum serum fluoride of only 5.6 μmol/L in healthy young patients undergoing prolonged plastic surgery (10). Slightly larger peak serum F^- concentrations (6.5 μmol/L) were reported in morbidly obese patients exposed to 2.5 MAC-hours of isoflurane (15). A few case reports have been published describing the use of prolonged isoflurane. A child who received 73 MAC-hours for status asthmaticus reached a peak plasma fluoride level of only 9.5 μmol/L (16), and a patient with status epilepticus who received 68 MAC-hours of isoflurane showed no increase in urinary F^- elimination (17). By contrast, a 2-yr-old girl treated with 107 MAC-hours of isoflurane for chorea achieved a peak fluoride concentration of 37 μmol/L, but she was also receiving phenytoin and barbiturates that may have affected isoflurane metabolism (18).

The patients in all these studies were relatively fit and healthy subjects, whereas those in our study were critically ill patients requiring ventilatory support in the ITU. In this study, a mean of 8.67 MAC-hours produced a mean maximum F^- concentration of 25.3 μmol/L. In a previous study in our unit, subanesthetic concentrations of isoflurane were used for sedation, and a mean of 2.84 MAC-hours produced a peak mean plasma concentration of 13.6 μmol/L (3). These results support our findings that in the critically ill there is a larger mean maximum plasma fluoride concentration than would be expected after the equivalent MAC-hours of anesthesia. The explanation for this is unclear, but there may be a difference in isoflurane metabolism during prolonged exposure. In Fischer rats in which a very low concentration of anesthetic was inhaled for a long period, the extent of biotransformation of isoflurane was found to be only slightly less than that of enflurane (19). It could be that the small extent of metabolism seen when it is used as an anesthetic agent is the result of its rapid exhalation in the postanesthetic period. Thus, less is available for metabolism than with agents that remain in the body longer. Previous studies after subanesthetic exposure to halothane have shown that anesthetic uptake by the liver was proportionately larger at the lowest concentrations. This may be a result of decreased liver blood flow at higher anesthetic concentrations, more efficient metabolism at lower concentrations, or a combination of these effects. There may be a more complex biotransformation of isoflurane after chronic exposure, which might explain the higher-than-expected fluoride levels seen in our patients.

Other important considerations known to affect drug metabolism include patient factors such as genetic variation, race, exercise, fasting, hepatic blood flow, hypoxia, and drugs; enzyme factors such as inducing agents, alcohol, age, sex, diet, and smoking habits; and factors such as solubility and dose of inhaled anesthetic. Our patients all had severe complex pathology, and the metabolism of isoflurane may have been altered by such factors as changes in hepatic blood flow, hypoxemia, drugs, and concurrent illnesses.

In our study, the plasma F^- concentration continued to increase after the isoflurane was discontinued, reaching a peak at a mean of 16 h later. This is consistent with previous work, although this peak occurred later than has been reported (3,14). The F^- concentration in the midazolam group reached a peak 12 h after starting sedation, which presumably reflects the long-duration of anesthesia many patients in this group received before their ITU admission. The concentration of F^- continues to increase in most studies after methoxyflurane, enflurane, and isoflurane anesthesia, although there is no clear explanation for this. Serum F^- increased more rapidly during methoxyflurane anesthesia in obese patients than in nonobese, and peak F^- concentrations were larger and occurred sooner after discontinuation of methoxyflurane in obese patients than in nonobese (20). In nine healthy male patients, F^- concentration continued to increase for 6 h after a mean of 4 h of isoflurane anesthesia (14), whereas in five morbidly obese female patients, F^- concentration continued to increase for 12 h after 2.5 MAC-hours of isoflurane (15). There appears to be an increased anesthetic biotransformation in obese patients. Despite the fact that isoflurane has a very low oil-gas solubility coefficient compared with other volatile anesthetics, a long exposure will lead to accumulation in fat. We were unable to show any correlation between the rate of increase in fluoride concentration after isoflurane sedation with the body weight of the patient. Although more is understood now about the distribution and elimination of inorganic fluoride in healthy subjects, in the obese and in patients with renal impairment, fluoride physiology in the bed-bound patient receiving ventilatory support and intensive therapy is largely unknown and difficult to evaluate.

After this initial increase in F^- concentration after discontinuing isoflurane administration, the concentration of inorganic fluoride decreased exponentially with a half-life of 111 h. This is considerably longer than has previously been shown with administration of methoxyflurane for 48 h (21) or with administration of isoflurane for 36 h (13). The difference between the anesthetics is related to the low lipid solubility of isoflurane. The urinary half-life of fluoride ions produced from a fluorinated anesthetic could be influenced by the duration of metabolism, which could explain the considerably longer half-life in our critically ill patients than was observed in fit, healthy patients (13).

In a controlled study in patients with mild to moderate preoperative renal dysfunction, enflurane administration was not associated with any deterioration in renal function (22). The mean peak postoperative F^- level of 19 μmol/L and its rate of decline were similar to values measured after enflurane anesthesia in patients with normal renal function. This is surprising because if renal F^- excretion were impaired, higher serum F^- levels might have been expected, which could cause further renal damage. The fact that this did not occur may be explained by extrarenal F^- redistribution primarily into bone (23). We were unable to show any correlation between the maximum fluoride concentration seen in each patient and creatinine concentration or any other measure of renal function, implying that the serum fluoride concentration obtained was independent of renal function. As there was no correlation with plasma fluoride and the APACHE II score, it appears that the plasma fluoride is also independent of the severity of illness.

The release of inorganic fluoride during metabolism of methoxyflurane was sufficient to cause renal toxicity (2,8), and this led to the withdrawal of methoxyflurane from human use. Because of certain similarities in chemical structure, enflurane and isoflurane also release inorganic fluoride (as a result of metabolism by cytochrome P450). Serum and urinary F^- levels are increased after enflurane anesthesia, but not to the extent implicated in the polyuric renal insufficiency associated with methoxyflurane metabolism (9). However, prolonged enflurane anesthesia has led to elevated fluoride concentrations and to evidence of impaired urine-concentrating ability (10,11). From urine samples taken over 72 h after anesthesia, Holaday et al. (12) calculated the overall biodegradation rate of isoflurane to be less than 0.2%, which is significantly less than for enflurane, making F^- nephrotoxicity unlikely even after prolonged exposure to isoflurane. However, it has recently been illustrated that isoflurane might be biotransformed much more than previously reported (13).

Inorganic fluoride concentrations in plasma larger than 50 μmol/L have been associated with a reduction in the kidney's ability to concentrate urine, although the exact figure remains controversial. It has been stated that plasma fluoride values as high as 100 μmol/L are safe (24,25), but a mean peak serum inorganic fluoride level of 33.6 μmol/L, with values above 20 μmol/L for 18 h has been shown to be nephrotoxic (11). Whether peak serum inorganic fluoride level is a more significant determinant of nephrotoxicity than is duration of elevation has not been established. Despite our high fluoride concentrations, no difference in renal function was observed between the groups. We chose creatinine clearance and urine osmolality as our most sensitive indices of renal function. It was not believed appropriate to do more specific and sensitive renal function tests, such as the response to vasopressin or inulin clearance in our patients, many of whom had a mild degree of renal dysfunction before and during the study. Many of the patients in both groups were receiving inotropes to maintain their cardiovascular system, low-dose dopamine to promote renal blood flow, and occasional diuretics to ensure an adequate diuresis. It was not possible to match the patients for diagnoses, making comparison between the groups difficult, but there was certainly no clinical impairment of renal function in the isoflurane group.

Although we found a significant ($P = 0.022$) linear relationship between the MAC-hours and the maximum F^-, the scatter was such ($R^2 = 18\%$) that it would be impossible to predict accurately how many MAC-hours of isoflurane could be administered before a potentially nephrotoxic level of serum F^- was reached. A correlation has been shown for methoxyflurane, and more than 2.5 MAC-hours produced levels of F^- of greater than 50 μmol/L. For isoflurane and enflurane, some studies have shown a correlation between dose and urinary F^- excretion (13,26); although in other series, no correlations have been found (2,10). Many factors such as the rate of urine output (27), acidity (28), and general acid-base balance (29) affect serum F^- concentrations and urinary F^- excretion. Urinary organic fluoride excretion might correlate better with isoflurane metabolism.

The dose of isoflurane administered to our patients was varied between 0.1% and 0.6% according to clinical signs to achieve sedation at the desired level. Tolerance to isoflurane has not been observed in mice chronically exposed to low concentrations of isoflurane for up to 63 days (30), and we did not observe any need to increase the inspiratory concentration of isoflurane to maintain the patient at a satisfactory level of sedation. There has only been one report of tolerance to isoflurane in a young child (18).

The results of this study show that subanesthetic concentrations of isoflurane can be used to provide prolonged sedation in patients receiving ventilatory support in the intensive therapy unit. Metabolism to inorganic fluoride does occur and larger levels of inorganic fluoride are seen than might be expected from the MAC-hours of isoflurane received, indicating altered isoflurane metabolism in these critically ill patients. Despite the increased plasma fluoride concentrations, we found no biochemical or clinical evidence of deterioration in renal function.

We thank Dr. John Tyler and the Medical Research Council Dental Group, Bristol Dental Hospital, for the use of their fluoride electrode system and for advice throughout the project. We are grateful to Anne Whitehead from the Department of Applied Statistics, University of Reading, for statistical assistance.

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Hypertonic/Hyperoncotic Fluid Resuscitation After Hemorrhagic Shock in Dogs

Donald S. Prough, MD, John M. Whitley, MD, PhD, Michael A. Olympio, MD,
Carol L. Taylor, MAS, and Douglas S. DeWitt, PhD

Departments of Anesthesia (Section on Critical Care), Neurology, Anatomy, and Public Health Sciences, Wake Forest University Medical Center, Winston-Salem, North Carolina

We compared canine systemic and cerebral hemodynamics after resuscitation from hemorrhagic shock with 4 mL/kg (a volume approximating 12% of shed blood volume) of 7.2% saline (HS; 1233 mEq/L sodium), 20% hydroxyethyl starch (HES) in 0.8% saline, or a combination fluid consisting of 20% hydroxyethyl starch in 7.2% saline (HS/HES). Eighteen endotracheally intubated mongrel dogs (18–24 kg) were ventilated to maintain normocarbia with 0.5% halothane in nitrous oxide and oxygen (60:40). After a 30-min period of hemorrhagic shock (mean arterial blood pressure = 40 mm Hg), extending from time T0 to T30, animals received one of three randomly assigned intravenous resuscitation fluids: HS, HES, or HS/HES. Data were collected at baseline, at the beginning and end of the shock period (T0 and T30), immediately after fluid infusion (T35), and at 60-min intervals for 2 h (T95, T155). After resuscitation, mean arterial blood pressure and cardiac output increased similarly in all groups, but failed to return to baseline. Intracranial pressure decreased during shock and increased slightly, immediately after resuscitation in all groups. During shock, cerebral blood flow (cerebral venous outflow method) declined in all groups. After resuscitation, cerebral blood flow increased, exceeding baseline in the HS and HS/HES groups but remaining low in the HES group ($P < 0.05$ HS vs HES at T35). We conclude that small-volume resuscitation (4 mL/kg) with HS, HS/HES, or HES does not effectively restore or sustain systemic hemodynamics in hemorrhaged dogs. In dogs without intracranial pathology, the effects on cerebral hemodynamics are also comparable, except for transiently greater cerebral blood flow in the HS group in comparison with the HES group.

(Anesth Analg 1991;73:738–44)

Prompt restoration of arterial blood pressure and cardiac output is essential in the acute resuscitation of trauma victims. Intravenous administration of fluids that effectively improve perfusion when given in small volumes are particularly attractive for resuscitation at the trauma scene or during emergency transport. Recently, infusion of small volumes of hypertonic salt solutions has been investigated. Velasco and colleagues stimulated renewed interest in hypertonic resuscitation when they reported that as little as 4.0 mL/kg of 7.5% saline restored systolic blood pressure and cardiac output and produced 100% survival in dogs subjected to hemorrhage that approximated half the estimated canine blood volume (about 40 mL/kg) (1–3). Subsequent investigators have confirmed that hypertonic saline, in a variety of concentrations, with and without added colloid, produces acute stabilization when administered in volumes much smaller than the original volume of shed blood (4–11). In addition to restoring systemic hemodynamic status, hypertonic solutions also reduce intracranial pressure (ICP) (8,9), an effect that may be advantageous in patients in whom cranial trauma complicates hemorrhagic shock.

Colloid, usually 6.0% low-molecular weight dextran, has been added to hypertonic solutions to extend the relatively short-lived hemodynamic effects (7,12–14). The most commonly used synthetic colloid in the United States is hydroxyethyl starch. Although several investigators have studied the effects of hypertonic saline in combination with 6% dextran, the systemic or cerebral effects of highly concentrated (20%) hydroxyethyl starch alone or in combination with hypertonic resuscitation solutions have not been

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Supported by Department of the Army, Medical Division, Contract 17-86-C-6181.

Presented in part at the Sixteenth Annual Educational and Scientific Symposium, Society of Critical Care Medicine, Anaheim, California, May 28, 1987.

Accepted for publication August 26, 1991.

Address correspondence to Dr. Prough, Section on Critical Care, Department of Anesthesia, Wake Forest University Medical Center, Winston-Salem, NC 27103.

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0003-2999/91/$3.50

investigated. For acute, small-volume resuscitation, more concentrated colloid solutions provide greater plasma volume expansion. Because viscosity and resistance to flow through intravenous catheters of hydroxyethyl starch solutions increase as concentrations increase, a 20% solution (in comparison with the commercially available 6% solutions) is the maximum practical concentration.

Therefore, we performed the following study to compare the effects on systemic and cerebral hemodynamics of acute resuscitation with 4.0 mL/kg of 7.2% saline (HS), 20% hydroxyethyl starch (HES) in 0.8% saline, or 20% hydroxyethyl starch in 7.2% saline (HS/HES).

Methods

Animals were handled according to guidelines established by the institutional Animal Care and Use Committee. Eighteen mongrel dogs of either sex, weighing 18–24 kg, were anesthetized with thiopental sodium (8.0 mg/kg IV), paralyzed with pancuronium (0.2 mg/kg IV), and endotracheally intubated. Halothane (0.5% in nitrous oxide and oxygen [60:40]) maintained anesthesia. Respiration was assisted using an Edco model 822 large-animal ventilator (Edco Scientific, Chapel Hill, N.C.), at a tidal volume of 15 mL/kg and a rate sufficient to maintain normocarbia (Pa_{CO_2}, 35–45 mm Hg). Additional pancuronium, given as needed, prevented respiratory movement.

Two femoral artery catheters were placed for monitoring of arterial blood pressure and for induction of rapid hemorrhage, respectively. A flow-directed pulmonary artery catheter, placed percutaneously via the right external jugular vein, measured cardiac output (CO) and pulmonary artery occlusion pressure. Hemodynamic pressure monitoring utilized a Grass 79D polygraph (Grass Instrument, Quincy, Mass.) with Gould-Statham P23 transducers (Gould, Oxnard, Calif.). Systemic and pulmonary artery pressures were recorded continuously; pulmonary artery occlusion pressure was measured intermittently. Cardiac output was recorded intermittently using an American Edwards 9520A CO computer (American Edwards, Santa Ana, Calif.). Body temperature was monitored continuously by a thermistor on the tip of the pulmonary artery catheter and was maintained near baseline values by applying a heating pad to the trunk and extremities. All transducers, except for ICP, were intermittently calibrated at the level of the left atrium.

Cerebral Blood Flow Measurement

After splenectomy (to prevent splenic autotransfusion during shock), animals were turned to the prone "sphinx" position and the occipital musculature was dissected from the underlying cranium. Cerebral blood flow (CBF) was measured using a modification of the technique originally described by Rapela and Green (15), in which the confluence of the sagittal sinus was cannulated and timed samples of cerebral venous outflow were measured. After cannulation of the confluence, occlusion of the lateral sinuses was confirmed by transient occlusion of the tubing through which cerebral venous outflow drained. An 18-gauge catheter inserted into the cisterna magna and zeroed to the level of the external auditory meatus (7 cm above left atrial level) provided continuous ICP monitoring.

Method of Hemorrhage

After instrumentation, all animals were left undisturbed for 30 min, after which baseline data were recorded. Recorded data consisted of CBF, systolic and diastolic arterial blood pressures (SAP and DAP), CO, pulmonary artery occlusion pressure, pulmonary arterial systemic and diastolic pressures, body temperature, arterial pH, Pa_{CO_2}, Pa_{O_2} (IL 1306; Instrumentation Laboratory, Lexington, Mass.), and hemoglobin (IL 282; Instrumentation Laboratory). Mean arterial blood pressure (MAP) and cerebral perfusion pressure (CPP) were calculated from the following formulas:

$$\mathrm{MAP} = \mathrm{DAP} + \frac{1}{3}(\mathrm{SAP} - \mathrm{DAP}), \qquad (1)$$

$$\mathrm{CPP} = \mathrm{MAP} - \mathrm{ICP}. \qquad (2)$$

After anticoagulation with heparin (500 IU/kg IV), blood was rapidly withdrawn through the right femoral artery catheter to reduce MAP to 40 mm Hg; MAP was maintained at that level for 30 min by removing or reinfusing shed blood. Hemodynamic data were obtained at the beginning and end of the shock period (T0 and T30), where T stands for time and the number following indicates the minutes elapsed since the onset of shock.

At the end of the shock interval, animals received one of three resuscitation fluids, which had been randomly assigned before each study using a table of random numbers: group HS (n = 6) received 4.0 mL/kg of 7.2% hypertonic saline (1233 mEq/L sodium), group HES (n = 6) received 4.0 mL/kg of 20% hydroxyethyl starch dissolved in 0.8% saline, and group HS/HES (n = 6) received 4.0 mL/kg of 20% hydroxyethyl starch dissolved in 7.2% saline. Additional data were collected immediately after infusion of the resuscitation fluid over 5 min (T35) and thereafter at hourly intervals for 2 h (T95, T155). After the experimental period, all brains were examined for

Table 1. Body Weight, Shed Blood, and Resuscitation Volumes

Group	*n*	Weight (kg)	Blood loss (mL/kg)	Resuscitation volume (mL/kg)
HS	6	20.7 ± 0.9	29 ± 2.3	4.0
HES	6	20.9 ± 1.0	31 ± 3.2	4.0
HS/HES	6	21.9 ± 1.2	36 ± 2.9	4.0

HS, 7.2% saline; HES, 20% hydroxyethyl starch in 0.8% saline; HS/HES, 20% hydroxyethyl starch in 7.2% saline.
Values are mean ± SEM.

evidence of subarachnoid, subdural, or epidural hemorrhage.

Statistical Analysis

All data were analyzed using SAS statistical software on a Vax 730 computer by a biostatistician coinvestigator (C.L.T.). The Kruskall-Wallis test was used to assess differences among the groups at baseline and during shock. A multivariate repeated measures analysis of variance was performed to determine if interactions between groups and time existed at subsequent postresuscitation intervals (16). Interactions were analyzed further with Holm's sequentially rejective multiple test procedure using a significance level of 0.05 (17). To assess time and group differences when an interaction was not present, a multivariate repeated measures analysis of variance and an analysis of covariance were performed on the dependent variables. When a statistically significant group effect was evident, Holm's sequentially rejective multiple test procedure was used to determine which groups differed.

Results

Mean body weight, shed blood volume, and resuscitation volume for the HS, HES, and HS/HES groups are listed in Table 1. Body weights and volumes of shed blood were similar among groups. All subsequent values in the text, tables, and figures are expressed as mean ± SEM.

Systemic Variables

Kruskal-Wallis testing detected no difference in MAP at baseline or during shock among the three groups (Figure 1A). Immediately after resuscitation, MAP increased similarly in all groups but remained well below baseline. By 120 min after resuscitation (T155), MAP had decreased in all groups to values similar to those present during shock (Figure 1A). Systolic arterial blood pressure and DAP were comparable among groups after resuscitation (Table 2).

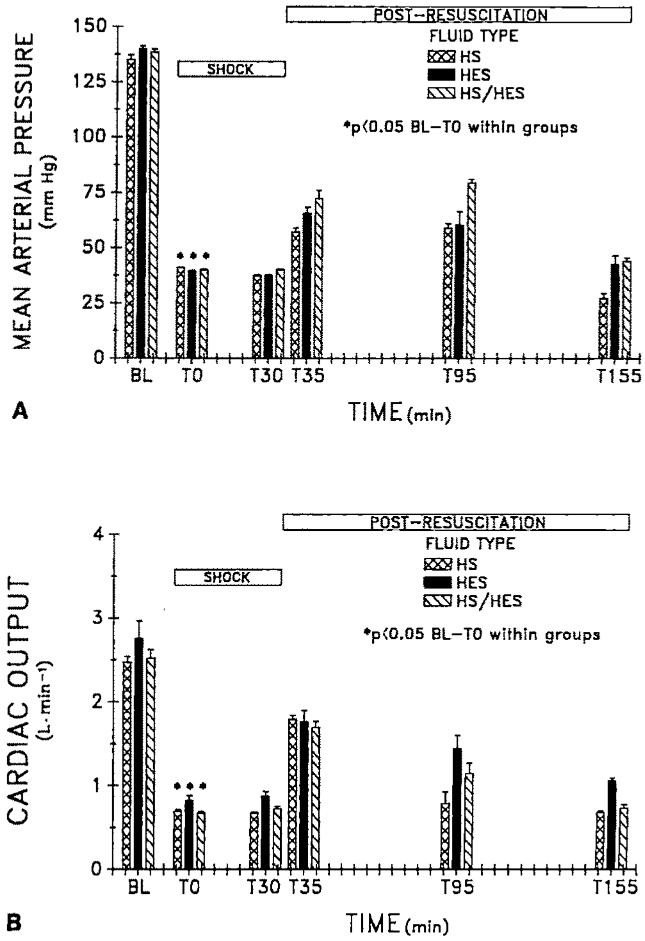

Figure 1. Changes in mean arterial pressure (**A**) and cardiac output (**B**) after resuscitation from hemorrhagic shock with 7.2% saline (HS), 20% hydroxyethyl starch in 0.8% saline (HES), or 20% hydroxyethyl starch dissolved in 7.2% saline (HS/HES). BL, baseline.

Cardiac output decreased by approximately 70% with induction of shock ($P < 0.05$ T0 compared to baseline). After resuscitation, CO increased approximately twofold in each of the three fluid groups (Figure 1B) but did not attain baseline values. This increase in CO at T35 was followed by a gradual decrease that continued throughout the postresuscitation period in all groups.

Pulmonary artery occlusion pressure, although decreased during shock, was comparable to baseline throughout the postresuscitation period (Table 2). Hemoglobin decreased in all three groups after resuscitation (Table 2). Other variables, including pH, $Paco_2$, Pao_2, and body temperature, were similar among groups at all time intervals (Table 3).

Cerebral Variables

Intracranial pressure was comparable among groups at baseline. Induction of shock decreased ICP signif-

Table 2. Major Systemic Variables

Variable	Group	BL	T0	T30	T35	T95	T155
SAP (mm Hg)	HS	169 ± 3	65 ± 4	56 ± 1	80 ± 4	87 ± 4	52 ± 4
	HES	178 ± 3	52 ± 5	56 ± 1	86 ± 3	85 ± 6	62 ± 6
	HS/HES	148 ± 5	52 ± 1	54 ± 1	96 ± 3	105 ± 1	65 ± 3
DAP (mm Hg)	HS	118 ± 2	33 ± 1	31 ± 1	38 ± 2	39 ± 3	22 ± 2
	HES	121 ± 1	32 ± 1	28 ± 1	48 ± 3	48 ± 6	33 ± 3
	HS/HES	120 ± 2	35 ± 1	33 ± 1	49 ± 5	66 ± 2	34 ± 1
PAOP (mm Hg)	HS	4 ± 0.3	3 ± 0.5	4 ± 0.5	3 ± 0.3	5 ± 0.4	3 ± 0.5
	HES	3 ± 0.2	2 ± 0.3	3 ± 0.3	4 ± 0.3	3 ± 0.6	4 ± 0.3
	HS/HES	3 ± 0.2	1 ± 0.3	3 ± 0.3	2 ± 0.2	3 ± 0.4	3 ± 0.4
Hgb (g/dL)	HS	12.2 ± 0.2	10.5 ± 0.2	9.7 ± 0.2	7.9 ± 0.2	7.5 ± 0.0	9.4 ± 0.2
	HS	11.8 ± 0.4	10.6 ± 0.3	10.2 ± 0.3	9.0 ± 0.2	8.4 ± 0.4	8.0 ± 0.4
	HS/HES	12.9 ± 0.3	10.9 ± 0.2	11.0 ± 0.5	8.6 ± 0.1	10.6 ± 0.1	8.1 ± 0.2

BL, baseline; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; PAOP, pulmonary artery occlusion pressure; Hgb, hemoglobin; HS, 7.2% saline; HES, 20% hydroxyethyl starch in 0.8% saline; HS/HES, 20% hydroxyethyl starch in 7.2% saline.
Values are mean ± SEM.

Table 3. Major Systemic Variables

Variable	Group	BL	T0	T30	T35	T95	T155
pH	HS	7.37 ± 0.0	7.41 ± 0.0	7.19 ± 0.0	7.05 ± 0.0	7.21 ± 0.0	7.13 ± 0.0
	HES	7.36 ± 0.0	7.40 ± 0.0	7.16 ± 0.0	7.10 ± 0.0	7.22 ± 0.0	7.19 ± 0.0
	HS/HES	7.37 ± 0.0	7.40 ± 0.0	7.21 ± 0.0	7.10 ± 0.0	7.28 ± 0.0	7.17 ± 0.0
$Paco_2$ (mm Hg)	HS	40 ± 0	30 ± 1	38 ± 1	51 ± 1	34 ± 1	33 ± 0
	HES	41 ± 1	31 ± 1	46 ± 2	49 ± 1	35 ± 1	34 ± 1
	HS/HES	39 ± 0	30 ± 1	39 ± 0	48 ± 1	33 ± 0	38 ± 1
Pao_2 (mm Hg)	HS	231 ± 2	216 ± 3	261 ± 15	243 ± 7	226 ± 2	226 ± 2
	HES	212 ± 7	208 ± 3	209 ± 5	217 ± 4	215 ± 2	210 ± 3
	HS/HES	235 ± 4	226 ± 4	222 ± 4	202 ± 7	224 ± 2	216 ± 4
Temp (°C)	HS	38 ± 0.2	38 ± 0.2	38 ± 0.1	38 ± 0.1	38 ± 0.1	37 ± 0.2
	HES	37 ± 0.1	37 ± 0.1	37 ± 0.2	37 ± 0.2	37 ± 0.2	38 ± 0.1
	HS/HES	37 ± 0.0	37 ± 0.1	37 ± 0.1	37 ± 0.0	38 ± 0.0	38 ± 0.1

BL, baseline; HS, 7.2% saline; HES, 20% hydroxyethyl starch in 0.8% saline; HS/HES, 20% hydroxyethyl starch in 7.2% saline.
Values are mean ± SEM.

icantly from baseline in all groups ($P < 0.05$). After resuscitation, ICP increased in all groups but did not increase to baseline values (Figure 2A). Intracranial pressure, like CBF, decreased gradually over time in all groups. Cerebral perfusion pressure followed the same general pattern as MAP (Figure 2B).

Cerebral blood flow at baseline was comparable among groups and decreased comparably among groups during shock. Kruskal-Wallis testing failed to detect a difference at baseline or during shock among groups. Resuscitation with HS increased CBF to greater than baseline values compared to HES, which produced only a slight increase in CBF ($P < 0.05$ HS vs HES at T35), and HS/HES (P = NS) (Figure 3). Although HS and HS/HES initially increased CBF, the increase was transient; CBF declined from T35 to T95 to a level that approximated CBF levels during shock. Cerebral blood flow in all three groups was comparable at T95 and T155.

Discussion

In the past decade, investigators have stimulated renewed interest in the applicability of small-volume resuscitation in hemorrhagic shock. Velasco and colleagues demonstrated that unanesthetized dogs, subjected to hemorrhage equal to approximately one half of estimated blood volume, could be effectively resuscitated using 7.5% saline in a dose of 4 mL/kg, a volume that was equal to about one tenth of the initial shed blood volume (3). They further demonstrated that hypertonic saline failed to improve systemic hemodynamics if a vagally mediated reflex arc were abolished or if hypertonic saline were infused into the aorta rather than into the inferior vena cava (1). Other investigators, using similar hemorrhagic shock preparations, have been unable to reproduce sustained improvements in blood pressure and CO using hypertonic saline alone (8–10). Because of the transient response to hypertonic saline alone, subsequent in-

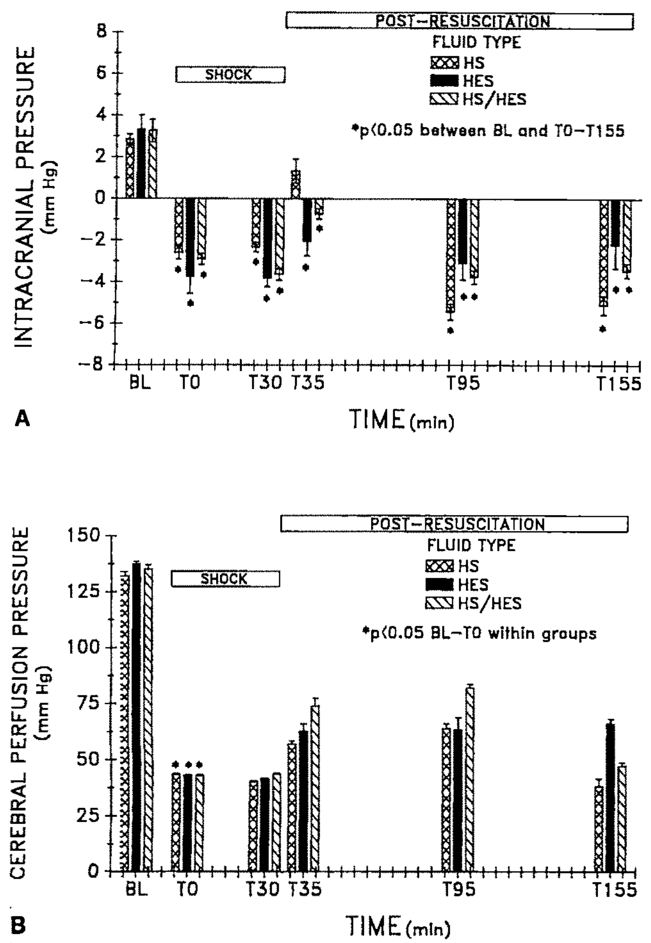

Figure 2. Changes in intracranial pressure (A) and cerebral perfusion pressure (B) after resuscitation from hemorrhagic shock with 7.2% saline (HS), 20% hydroxyethyl starch in 0.8% saline (HES), or 20% hydroxyethyl starch dissolved in 7.2% saline (HS/HES). BL, baseline.

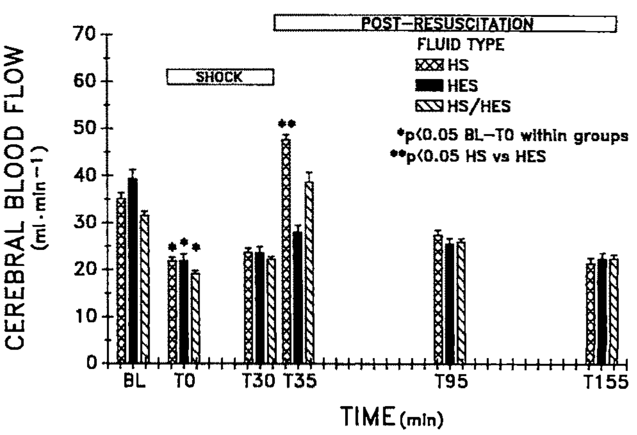

Figure 3. Changes in cerebral blood flow after resuscitation from hemorrhagic shock with 7.2% saline (HS), 20% hydroxyethyl starch in 0.8% saline (HES), or 20% hydroxyethyl starch dissolved in 7.2% saline (HS/HES). BL, baseline.

vestigators added a colloid component, usually 6.0% low–molecular weight dextran, to extend the effect of hypertonic saline (7,10,12–14).

Our data demonstrate that each of the three resuscitation fluids produce comparable, short-term systemic hemodynamic improvement. However, when administered in equal volumes of 4.0 mL/kg, all fail to restore and maintain MAP and CO after the immediate postresuscitation interval. These data differ significantly from previous studies of hypertonic saline alone or combined with dextran. Velasco et al. successfully resuscitated 100% of dogs using 4 mL/kg of 7.5% saline after hemorrhage to 50% of estimated blood volume (3). After more severe hemorrhage (i.e., MAP = 35 mm Hg for 30 or 60 min), resuscitation with 6 mL/kg of 7.5% saline alone failed to produce 100% survival in mongrel dogs (14). Mean arterial blood pressure was better maintained in animals that received 6.0 mL/kg of 7.5% saline combined with 6.0% dextran despite similar expansion of plasma volume and similar increases in plasma sodium. Although either hypertonic saline alone or hypertonic saline combined with 6% dextran produced comparable short-term resuscitation, the combination fluid better sustained MAP in animals shocked for either 30 or 60 min.

The failure to demonstrate sustained systemic hemodynamic improvement after resuscitation with either hypertonic saline or the combination fluid may relate to differences in experimental design. First, we more rapidly exsanguinated animals, reducing MAP to 40 mm Hg in approximately 5 min, rather than the 15-min interval used by Velasco et al. (14). Second, all animals in the present study were splenectomized, a procedure that limits the canine compensatory response to hemorrhage. Splenectomy, generally considered to be a necessary prelude to hemorrhage in canine models, was not performed in Velasco's study. Third, we infused fluid into a forelimb vein rather than the femoral vein, although peripheral and central infusions appear to be equivalent (18). Fourth, and most important, animals in the present study were anesthetized, paralyzed, and provided controlled ventilation. The effects of mechanical ventilation on preload and CO may have influenced the systemic response both to hemorrhage and the resuscitation fluids. In contrast, dogs in the study of Velasco et al. were intubated but breathed spontaneously.

The present study suggests that the combination of 7.2% saline and 20% hydroxyethyl starch in a dose of 4.0 mL/kg, unlike a similar volume of the combination of hypertonic saline with 6.0% low–molecular weight dextran, minimally prolongs the duration of systemic hemodynamic improvement. In contrast, Kramer et al. (12) bled unanesthetized adult sheep to a MAP = 50 mm Hg for 3 h (shed blood volume = 42

± 7 mL/kg), then resuscitated the animals with 200 mL of either 0.9% saline or 7.5% saline with 6% dextran-70. Only the combination fluid restored blood pressure and CO. The group that had received the combination fluid subsequently required only one-sixth the quantity of lactated Ringer's solution required by the isotonic saline group. In contrast, in the present study, neither 7.2% saline alone, 20% HES in 0.8% saline alone, nor the combination of 20% HES in 7.2% saline restored MAP. Methodologic differences between the two studies include choice of species (sheep vs dogs), anesthesia (unanesthetized vs anesthetized), and ventilatory management (spontaneous vs controlled).

Two more recent studies have demonstrated that hypertonic saline in combination with colloid is associated with superior survival in comparison with 0.9% saline or 7.5% saline in similar volumes. Maningas et al. (13) studied the effects of 0.9% saline, 7.5% saline, 6.0% dextran-70, or 7.5% saline in 6.0% dextran-70, each given in a volume equal to 25% of the shed blood volume after lethal hemorrhage in swine. The combination fluid was associated with 100% survival for 96 h in comparison with significantly poorer survival in the groups that received 0.9% saline or 7.5% saline. Velasco et al. (14) demonstrated that the combination of 7.5% saline and 6.0% dextran-70 was associated with somewhat higher survival and more sustained improvement in plasma volume than similar volumes of 6.0% dextran-70 or 7.5% saline alone.

As expected, ICP decreased in all groups during shock. Resuscitation resulted in small, transient increases in ICP above shock levels in all groups. Although CPP remained comparable among groups, CBF was significantly greater in the HS group than in the HES group immediately after resuscitation, although in all groups CBF had decreased to levels comparable to those during shock by 60 min after resuscitation. The initial improvement in CBF in the HS group could represent a primary cerebral vasodilator effect of acute hypertonicity (19,20) or it could result from lower blood viscosity.

A role for small-volume resuscitation in hemorrhagic shock in humans has yet to be demonstrated. In patients who suffer traumatic shock unaccompanied by head injury, small-volume resuscitation appears to offer few advantages over conventional resuscitation, assuming that patients are rapidly transported to hospitals for definitive treatment. The potential value of small-volume resuscitation solutions may be greater in situations involving mass casualties or in geographically remote areas in which evacuation is less rapid. Experimental data suggest the possibility that hypertonic solutions, with or without added colloid, may be useful for acute resuscitation of patients with combined head injury and hemorrhagic shock. In such patients, lower ICP (if accompanied by greater CPP) and improved CBF might be associated with improved neurologic outcome.

These data complement previous data from this laboratory, in which 6.0 mL/kg of 7.2% saline and 60 mL/kg of lactated Ringer's solution produced comparable restoration of CBF after hemorrhagic shock (9). Taken together, these studies suggest that small volumes of hypertonic fluid or large volumes of slightly hypotonic fluid produce comparable increases in CBF, although ICP is far greater after the latter fluid (9). Intracranial pressure is similar if small volumes of hypertonic fluid, hyperoncotic fluid, or the combination are given, but CBF is improved most by hypertonic fluid. Adding hypertonic saline to concentrated colloid results in an intermediate level of improvement in CBF.

Based on the data presented, we conclude that highly concentrated colloid solutions in combination with HS require further investigation as alternatives to hypertonic saline or concentrated colloid alone for small-volume resuscitation after trauma, especially if head injury accompanies hemorrhagic shock. Although the volumes administered in the current study were insufficient to fully restore systemic hemodynamics, short-term improvement, coupled with improved CBF, might be satisfactory pending definitive resuscitation.

We gratefully acknowledge the excellent secretarial assistance of Kim Barnes and the editorial review by Faith McLellan.

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Nitroprusside-Induced Hypotension and Cerebrovascular Autoregulation in the Anesthetized Pig

Kristina Stånge, MD, PhD, Michael Lagerkranser, MD, PhD, and Alf Sollevi, MD, PhD

Departments of Anesthesiology and Intensive Care and Experimental Surgery, Karolinska Institute, Stockholm, Sweden

The influence of sodium nitroprusside (SNP) on cerebral blood flow and cerebrovascular autoregulation at doses that produced 36% ± 3% (slight) and 52% ± 4% (moderate) reductions of mean arterial blood pressure (MABP) was evaluated in mechanically ventilated fentanyl/N_2O-anesthetized pigs. The blood flow of the frontal hemispheres was evaluated by sagittal sinus outflow, which was determined by an electromagnetic method. Integrity of cerebral autoregulation was evaluated by two formal tests: one hypertensive challenge with an angiotensin infusion ($n = 12$) and one hypotensive challenge with reduced venous return to the heart (blockade of the vena cava, $n = 7$). The tests were performed before, during, and after hypotension. Cerebral blood flow tended to increase during hypotension, but this change was not significant. Impaired autoregulation was seen in both tests during slight hypotension (MABP = 89 ± 3 mm Hg) with an SNP infusion of 12 ± 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Cerebral autoregulation was completely abolished at both tests during moderate hypotension (MABP = 61 ± 2 mm Hg with an SNP infusion of 38 ± 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Despite a posthypotensive increase in cerebral blood flow without rebound hypertension, the autoregulatory response to angiotensin-induced hypertension was restored within 15–25 min. The autoregulatory response to a decrease in MABP was impaired for more than an hour after discontinuation of the SNP infusion. No acidosis was observed. The authors conclude that during slight and moderate SNP-induced hypotension, there was a dose-dependent impairment of cerebral autoregulation. Further, the autoregulatory response to the hypotensive challenge after SNP hypotension was markedly delayed, whereas the response to hypertension was rapidly restored.

(Anesth Analg 1991;73:745–52)

The vasodilatory property of sodium nitroprusside (SNP), which leads to a reduction of the peripheral vascular resistance, is frequently used to reduce systemic arterial blood pressure during episodes of acute systemic hypertension or during surgical procedures that require controlled hypotension. In all forms of controlled hypotension, the risk of cerebral hypoxia owing to hypoperfusion must be recognized, and therefore knowledge of its effects on cerebral blood flow (CBF) is essential. During SNP-induced hypotension in anesthetized patients, the CBF remains essentially unaffected to mean arterial blood pressures (MABPs) of 50–55 mm Hg (1–4). This absence of changes in CBF has been attributed to an intact cerebral autoregulation (2,5,6) but could also be explained by a direct vasodilating effect of SNP on the vascular smooth muscle. This distinction is of importance as MABP variations owing to such factors as hemorrhage and stress reactions during induced hypotension could markedly influence the CBF if cerebral autoregulation is impaired. To evaluate cerebral autoregulatory responses during changes in MABP, the latter has to be altered by methods or drugs that exert no direct effects on the cerebral vessels (7,8). Such tests have indicated a disturbed cerebral autoregulatory response to an increase in MABP during SNP-induced hypotension in goats (9), baboons (8), and cats (10), as well as after SNP-induced hypotension in baboons (11) and cats (12). Little is known, however, about the impact of SNP-induced hypotension on the cerebrovascular responses to decreases in blood pressure, and the same applies to the influence of the SNP dosage on cerebral autoregulation.

This study was designed to evaluate the cerebrovascular responses to blood pressure manipulations (i.e., cerebral autoregulation) during SNP infusions in the fentanyl/N_2O-anesthetized pig. Autoregulatory tests

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This study was supported by grants from the Karolinska Institute, the Swedish Medical Research Council (Project No. 14X-7485), and the Swedish Association against Heart and Chest Diseases.

Accepted for publication August 13, 1991.

Address correspondence to Dr. Stånge, Department of Anesthesiology and Intensive Care, Karolinska Hospital, S-104 01 Stockholm, Sweden.

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0003-2999/91/$3.50

were conducted before, during, and after two levels of SNP-induced hypotension. The present preparation and anesthesia have previously been used for the evaluation of cerebral hemodynamic responses to other vasoactive drugs like adenosine and isoflurane (13,14).

Methods

Twelve young pigs were studied after approval had been received from the Swedish National Animal Investigation Committee. The animals (22.5 ± 0.7 kg, mean 21–30 kg, Swedish native breed) were premedicated with intramuscular ketamine (15–20 mg/kg) and atropine (0.03 mg/kg). Anesthesia was induced by pentobarbital (15–20 mg/kg IV), whereafter the trachea was intubated. Ventilation was controlled by an Engström respirator (Engström 200, Engström Medical, Sweden) with nitrous oxide in 25%–30% oxygen. The end-tidal CO_2 concentration was monitored by a CO_2 analyzer (CD 300, Datex, Finland). The minute ventilation was adjusted, when necessary, to keep arterial blood gas tensions normal. Anesthesia was maintained by an infusion of fentanyl (0.025 $mg \cdot kg^{-1} \cdot h^{-1}$) given after a bolus dose of 0.1 mg/kg over 10–15 min. Pancuronium, 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$, was given for paralysis after a bolus dose of 0.3 mg/kg. Body temperature was kept between 37°C and 39°C by means of blankets and heating lamps.

The animals were placed in a right-sided position. A catheter was introduced into the aorta through a femoral artery. It was used for recordings of and withdrawal of blood samples for analysis of arterial blood gases. A balloon-tipped catheter was inserted through a femoral vein and advanced to the right atrium. The balloon was inflated with 2 mL of saline. As the catheter was slowly retracted, the inferior vena cava was gradually occluded, resulting in a reduced cardiac output. This procedure (caval block) allowed a graded reduction of arterial blood pressure. The catheter was also used for infusion of angiotensin. The rapid variations in the end-tidal CO_2 concentration, resulting from changes in the cardiac output, were avoided by adjusting the minute ventilation.

Blood flow from the superior sagittal sinus was measured and regarded as the regional cerebral blood flow (rCBF) from the frontal hemispheres, a procedure previously described in detail (13). After intravenous heparin (10,000 IU followed by 2500 IU/h), a catheter (1.3-mm internal diameter) was introduced into the sagittal sinus and passed anteriorly about 5 mm. This catheter was connected to a larger sized one (3.0-mm internal diameter) and inserted into the superior vena cava through the external jugular vein. In this sinocaval shunt were incorporated an electromagnetic flow probe (Nycotron, Norway), connections for sagittal sinus pressure (SSP) recordings, and a side port for the collection of blood samples. Mean arterial blood pressure, SSP, rCBF, and end-tidal CO_2 concentrations were recorded continuously on a Grass polygraph (Grass Instrument Co., Quincy, Mass.). The zero reference for the pressure transducers was set at the midbrain level. To assure that the sagittal sinus blood flow reflects drainage only from cerebral tissue, the following experiment was performed in an additional animal. The concentration of the inspired CO_2 was varied and a threefold increase in rCBF was found together with unchanged regional cerebral metabolic rate ($rCMRo_2$) when $Paco_2$ was increased from 18 to 48 mm Hg. The animals were killed with intravenous potassium chloride after the experiments.

When rCBF had become stabilized, approximately 1 h after completing the preparation, blood samples were collected from the aorta and the sagittal sinus for blood gas determinations and calculation of the $rCMRo_2$. Cerebral autoregulation was then studied, first during an elevation of MABP to 20–60 mm Hg above basal values by the intravenous infusion of the short-acting drug angiotensin (Hypertensin, CIBA), a drug with no direct effect on cerebral vascular tone (15). The infusion rate was first set at 0.3 μg/min and, if necessary, increased to obtain the desired blood pressure level after 3–4 min, thereby allowing autoregulation to act (16). The upper limit of autoregulation ("breakthrough") was not tested because of the risk of causing damage to the cerebral vessels (17,18). When MABP and the rCBF were again stabilized after discontinuation of the angiotensin infusion (~10 min), autoregulation was studied during a decrease in MABP, achieved by caval block (performed in the last seven experiments). Mean arterial blood pressure was gradually reduced to 35–40 mm Hg. The time for this procedure ranged from 2 to 11 min. The autoregulatory response to the reduction in blood pressure, as well as the lower blood pressure limit of autoregulation, was determined. Thereafter, the caval block was slowly released, thus avoiding a marked overshoot in CBF.

Slight hypotension was induced by intravenous infusion of SNP (0.5 mg/mL, Nipride, Roche) to an MABP of approximately 90 mm Hg in seven pigs. When the desired level of blood pressure was stabilized (11 ± 2 min) the angiotensin test was performed and thereafter the caval block. All pigs were subjected to a *moderate hypotension* (MABP about 60 mm Hg) achieved by increasing the SNP infusion rate. At this hypotensive level, samples for blood gas analyses were collected and the autoregulation tests were repeated. The average duration of the administration of SNP was 52 ± 6 min (n = 12). The angiotensin test was repeated 15–25 min (n = 11) and 30–50 min (n = 10) after termination of the SNP infusion. The caval blocks were performed after each angiotensin test.

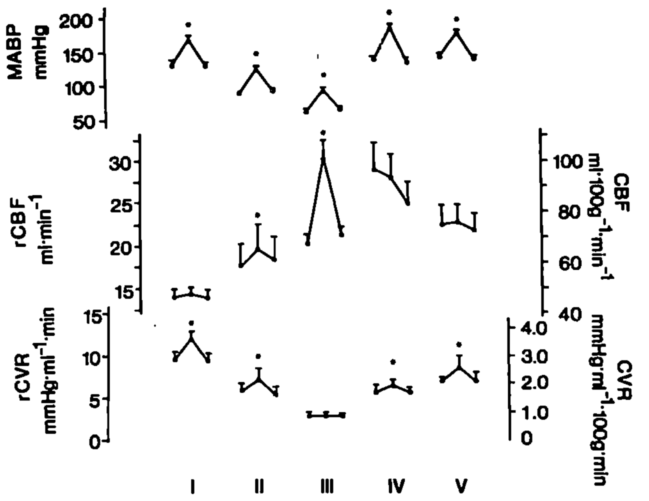

Figure 1. Regional cerebral blood flow (rCBF) and vascular resistance (rCVR) in anesthetized pigs before (I, $n = 12$) and during sodium nitroprusside infusion, causing light hypotension (II, $n = 7$) and moderate hypotension (III, $n = 12$), as well as 15–25 min after hypotension (IV, $n = 11$) and 30–50 min (V, $n = 11$) after hypotension. For each situation, values are given for before, during, and after the influence of an angiotensin-induced increase in mean arterial blood pressure (MABP). Mean ± SEM. $^*P < 0.05$, significant difference from the preangiotensin value. The values for 100 g tissue are estimates based on the mean weight of the drained regional tissue (≈30 g).

Cerebral perfusion pressure was calculated as MABP − SSP. Regional cerebrovascular resistance (rCVR) was calculated as cerebral perfusion pressure divided by rCBF. Oxygen saturation (SO_2) was derived from the formula $z^{2.64}/(4.08^{2.64} + z^{2.64})$, where 2.64 is the Hill coefficient for the pig (19) and 4.08 (kPa) is the P_{50} value for the pig (20). z is the Po_2 value corrected for pH; $z = Po_2 \times 10^{[-0.35(7.4-pH)]}$, where −0.35 is the Bohr factor for the pig (19). The oxygen content was calculated as $Hb{\cdot}So_2{\cdot}1.34 + Po_2{\cdot}0.23$ and the regional cerebral metabolic rate of oxygen ($rCMRo_2$) as rCBF multiplied by the arteriosagittal sinus difference of oxygen content. Regional cerebral blood flow corresponds to approximately 30 g brain weight (~40% of the total brain weight) with this preparation (13). For comparison, values for 100 g brain weight have also been *estimated* for CBF and cerebral vascular resistance in Figure 1.

Regional cerebrovascular resistance decreased in a linear pattern during the caval block ($P < 0.05$ in 23 of 26 regression calculations). Linear regression lines were calculated (MABP = A + B·rCVR) by determination of rCVR at various levels of reduced MABP down to an MABP level where rCVR did not further decrease (Figures 4 and 5). The slopes of the regression lines were statistically evaluated. The MABP level with the lowest value of rCVR was regarded as the lower limit of autoregulation.

Mean values and the standard error of the mean (SEM) are given. A general linear model type of variance analysis was used. The means for different variables were used for pairwise comparisons either with Tukey's (for unequal cell sizes) or Bonferroni's multiple-range test. Student's *t*-test was used for the evaluation of paired differences. A probability level below 0.05 was regarded as statistically significant.

Results

Effect of Sodium Nitroprusside on Regional Cerebral Blood Flow, Regional Cerebrovascular Resistance, and Regional Cerebral Metabolic Rate

Slight hypotension induced by an SNP infusion of 12 ± 3 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ (6.0–23.0 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$)

Table 1. Mean Arterial Blood Pressure, Cerebral Perfusion Pressure, Sagittal Sinus Pressure, Regional Cerebral Blood Flow, Vascular Resistance, and Metabolism Before, During, and After Hypotension Induced by Sodium Nitroprusside in Pigs

		Sodium nitroprusside			
	Control ($n = 12$)	Slight hypotension ($n = 7$)	Moderate hypotension ($n = 12$)	15–25 Min after SNP ($n = 12$)	30–50 Min after SNP ($n = 12$)
MABP (mm Hg)	133 ± 7	89 ± 3^a	61 ± $2^{a,b}$	141 ± $3^{b,c}$	144 ± $5^{b,c}$
CPP (mm Hg)	126 ± 7	85 ± 3^a	56 ± $2^{a,b}$	133 ± $6^{b,c}$	136 ± $5^{b,c}$
SSP (mm Hg)	7 ± 1	4 ± 1^a	5 ± 1	8 ± $1^{b,c}$	7 ± $1^{b,c}$
rCBF (mL/min)	14.1 ± 1.0	17.6 ± 2.6	20.1 ± 1.4	27.6 ± $3.3^{a,b,c}$	22.0 ± 2.1^a
rCVR (mm $Hg{\cdot}mL^{-1}{\cdot}min$)	9.6 ± 0.9	5.8 ± 1.1^a	3.0 ± 0.3^a	5.7 ± $0.8^{a,c}$	7.1 ± 1.0^c
$rCMRo_2$ (mL/min) ($n = 6$)	0.72 ± 0.13		0.95 ± 0.18	0.91 ± 0.20	

MABP, mean arterial blood pressure; CPP, cerebral perfusion pressure; SSP, sagittal sinus pressure; rCBF, regional cerebral blood flow; rCVR, regional cerebrovascular resistance; $rCMRo_2$, regional cerebral metabolic rate of oxygen; *n*, number of animals for each test solution.

Values are mean ± SEM.

[a] Significant differences ($P < 0.05$) compared with control.

[b] Significant differences ($P < 0.05$) compared with slight hypotension.

[c] Significant differences ($P < 0.05$) compared with moderate hypotension.

Table 2. Arterial pH, Po$_2$, and Pco$_2$ Before, During, and After Two Levels of Hypotension Induced by Sodium Nitroprusside

		Sodium nitroprusside			
	Control (n = 12)	Slight hypotension (n = 5)	Moderate hypotension (n = 11)	15–25 Min after SNP (n = 11)	30–50 Min after SNP (n = 10)
pHa	7.44 ± 0.01	7.41 ± 0.02	7.43 ± 0.01	7.40 ± 0.02[a,b]	7.42 ± 0.02
Pao$_2$ (mm Hg)	114 ± 4	106 ± 8	105 ± 6	102 ± 6	110 ± 7
Paco$_2$ (mm Hg)	40 ± 1	40 ± 1	39 ± 1	41 ± 1	40 ± 1
Hemoglobin (g/L)	112 ± 4 (n = 9)	108 ± 8 (n = 5)	104 ± 4[a] (n = 9)	109 ± 3 (n = 9)	111 ± 4 (n = 8)

n, Number of animals for each test solution.
Values are mean ± SEM.
[a] Significant differences ($P < 0.05$) compared with control.
[b] Significant differences ($P < 0.05$) compared with moderate hypotension.

caused a 36% ± 3% reduction in MABP and a 45% ± 9% decrease in rCVR. The rCBF tended to increase (28% ± 12%). Sagittal sinus pressure was reduced from 7 ± 1 to 4 ± 1 mm Hg (Table 1).

Moderate hypotension (MABP 52% ± 4% below baseline levels) was achieved by an SNP infusion of 37.7 ± 7.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (12.8–65.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Regional cerebrovascular resistance decreased 66% ± 5% below baseline levels and 46% ± 7% during slight hypotension. The increase in rCBF (48% ± 12%) did not reach statistical significance, although it was marked in six of the animals. There were difficulties in maintaining the systemic blood pressure in 7 of the 12 animals because of tachyphylaxis. When the angiotensin test was performed, the infusion rate amounted to 47 ± 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The total dose in the five animals subjected only to moderate hypotension was 1.4 ± 0.2 mg/kg, and in the seven animals subjected to both slight and moderate hypotension it was 1.3 ± 0.2 mg/kg (range 0.6–2.5 mg/kg in all animals). Regional cerebral metabolic rate was not increased and the arteriosagittal sinus difference of oxygen content (data not shown) was unaffected by the SNP infusion (n = 6).

After discontinuation of the SNP infusion, no rebound hypertension was observed. A marked increase in rCBF (111% ± 23%) was recorded 15–25 min posthypotensively and after 35–50 min it was still increased (57% ± 15%). In four animals the increase in rCBF was marked (177% ± 40%), declining after 10–15 min. These pigs had the highest infusion rates and total dose of SNP during the hypotension.

During the experiment, Paco$_2$ was kept at normocapnic levels and Pao$_2$ was not affected (Table 2). pHa was somewhat below baseline levels after the hypotension but remained within normal limits in all animals (Table 2).

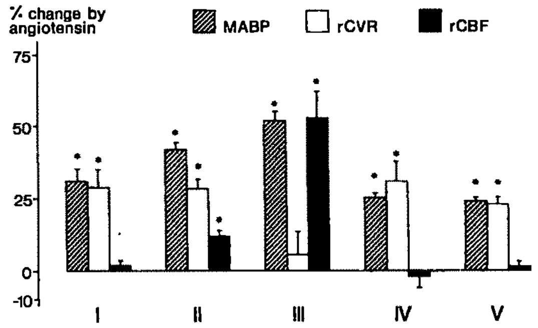

Figure 2. Percent changes in mean arterial blood pressure (MABP), regional vascular resistance (rCVR), and regional cerebral blood flow (rCBF) induced by angiotensin, before (I, n = 12) and during sodium nitroprusside infusion, causing light (II, n = 7) and moderate hypotension (III, n = 12) as well as 15–25 min (IV, n = 11) and 30–50 min (V, n = 11) after termination of the infusion of sodium nitroprusside. *$P < 0.05$, significant difference from the preangiotensin value in each situation.

Effect of Sodium Nitroprusside on Cerebral Autoregulation

Angiotensin test. The average increase in MABP during the tests was 31–37 mm Hg (highest before and lowest during high dose of SNP) (Figures 1 and 2). Before SNP was given, MABP increased 30% ± 4% and rCVR increased 29% ± 6% while rCBF remained unchanged after the infusion of angiotensin. In the seven animals subjected to *slight* hypotension, angiotensin caused a 42% ± 2% increase in MABP, along with a 12% ± 2% increase in rCBF and a 28% ± 3% increase in rCVR. During SNP-induced *moderate* hypotension, infusion of angiotensin resulted in a 52% ± 3% increase in MABP with a 53% ± 9% increase in rCBF while rCVR remained unaffected, which demonstrates a loss of cerebral autoregulation. During the two angiotensin tests after discontinuation of SNP, rCBF remained unchanged during increases in rCVR (31% ± 6% and 23% ± 2%, respectively).

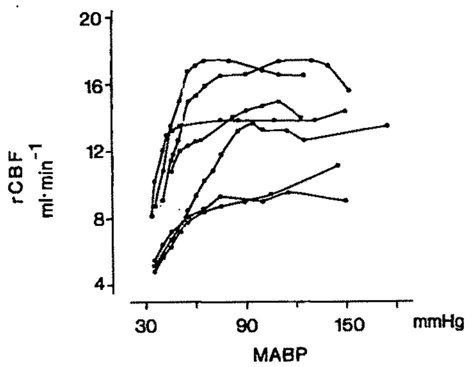

Figure 3. Regional cerebral blood flow (rCBF) in seven anesthetized pigs during reduction in mean arterial blood pressure (MABP) by graded inhibition of the venous return (vena caval blockade, control situation).

Vena caval blockade. Before SNP the average rCBF was not affected down to an MABP of 40–85 mm Hg produced by vena caval blockade. However, in two animals there were decreases in both rCBF (35%) and rCVR (47%) down to 50 mm Hg, whereupon rCVR did not decrease further (Figures 3 and 4). The lower limit of autoregulation before the administration of SNP averaged 54 ± 6 mm Hg with an rCVR of 4.7 ± 0.6 mm Hg·mL^{-1}·min and an rCBF of 12.0 ± 1.4 mL/min. During *slight* SNP-induced hypotension (MABP = 96 ± 3 mm Hg when the caval block was started [n = 7]), rCVR decreased until an MABP level of 60 ± 5 mm Hg (lower limit) was reached. At this level rCVR was 4.3 ± 0.7 mm Hg·mL^{-1}·min (Figure 4) and rCBF 15.2 ± 2.4 mL/min. The average slope of the regression lines (0.047 ± 0.006) was reduced compared with the regression lines before the administration of SNP (0.063 ± 0.004) (Figures 4A, 4B, and 5). During *moderate* hypotension (MABP = 70 ± 6 mm Hg, when the caval block was started), the rCBF was pressure-dependent with no reaction in rCVR (Figure 4C). The mean of the lowest calculated rCVR values was 2.7 ± 0.4 mm Hg·kg^{-1}·min. This rCVR level was significantly lower than the corresponding value during caval block, both before and during slight hypotension.

The rCVR reactivity to caval block at 20–30 min (Figure 4D) and 45–65 min after SNP hypotension had slightly recovered but was still significantly impaired compared with baseline (slope 0.032 ± 0.005 and 0.027 ± 0.004, respectively, Figure 5). In the two tests of the autoregulatory response to blood pressure decrease, the lower limit of autoregulation was at an MABP of about 70 mm Hg (Table 3). At this lower limit, rCVR did not differ from that seen before the administration of SNP (4.1 ± 0.9 and 4.3 ± 1.4 mm Hg·mL^{-1}·min, respectively), but the rCBF of about 20 mL/min and also the lower limit were significantly greater.

Discussion

The cerebrovascular autoregulatory responses to increases in MABP (angiotensin infusion) were normal before the administration of SNP (Figures 1 and 2). When cerebral autoregulation was challenged by a blood pressure decrease (caval block), rCBF was also essentially preserved (Figure 3) and rCVR was gradually reduced down to an MABP level of about 55 mm Hg (Figure 4A). This lower limit of autoregulation was similar to that obtained in anesthetized piglets during hemorrhage (21,22) and corresponds also to the lower limit found in humans (23). On the other hand, the rCBF was markedly affected when tested by rapid changes in systemic blood pressure as well as by alterations in $Paco_2$ levels (data not presented). The present protocol with normocapnia and slow artificial changes of MABP in the fentanyl/N_2O-anesthetized pig therefore provided conditions that allow for evaluation of autoregulatory function during administration of SNP. The sagittal sinus outflow technique provided for continuous CBF measurements and has previously been used in dogs (16,24), baboons (25), and piglets (26). The high doses of SNP and problems with tachyphylaxis may be explained by the anesthetic technique, with high doses of fentanyl and devoid of α-blocking agents, which increase the peripheral resistance.

During SNP-induced *moderate* hypotension (MABP ≈ 60 mm Hg), with no significant change in rCBF per se, infusion of angiotensin did not affect rCVR, and thus rCBF increased in parallel with the increase in systemic blood pressure. Caval block also resulted in a completely pressure-dependent decrease in rCBF with unaffected rCVR. This lack of change in rCVR suggests a loss of the cerebral autoregulatory response to blood pressure fluctuations at this hypotensive level. A disturbed cerebrovascular response to blood pressure increases during SNP-induced hypotension has previously been reported in anesthetized baboons (8), anesthetized cats (10), and awake goats (9).

It is noteworthy that the rCVR obtained during SNP-induced moderate hypotension was significantly lower than the rCVR at the lower limit of autoregulation both before and after hypotension (Figure 4). This illustrates that SNP administration can induce a stronger cerebral vasodilation per se than the autoregulatory mechanism. A direct cerebral vasodilatory effect of SNP has previously been demonstrated by several investigators. When administered directly into a cerebral artery, SNP increases CBF in goats (9), intracranial pressure in cats (10), and the diameter of the canine basilar artery (27). Also when topically applied, SNP dilates feline pial vessels (28). It is therefore suggested that the maintenance of

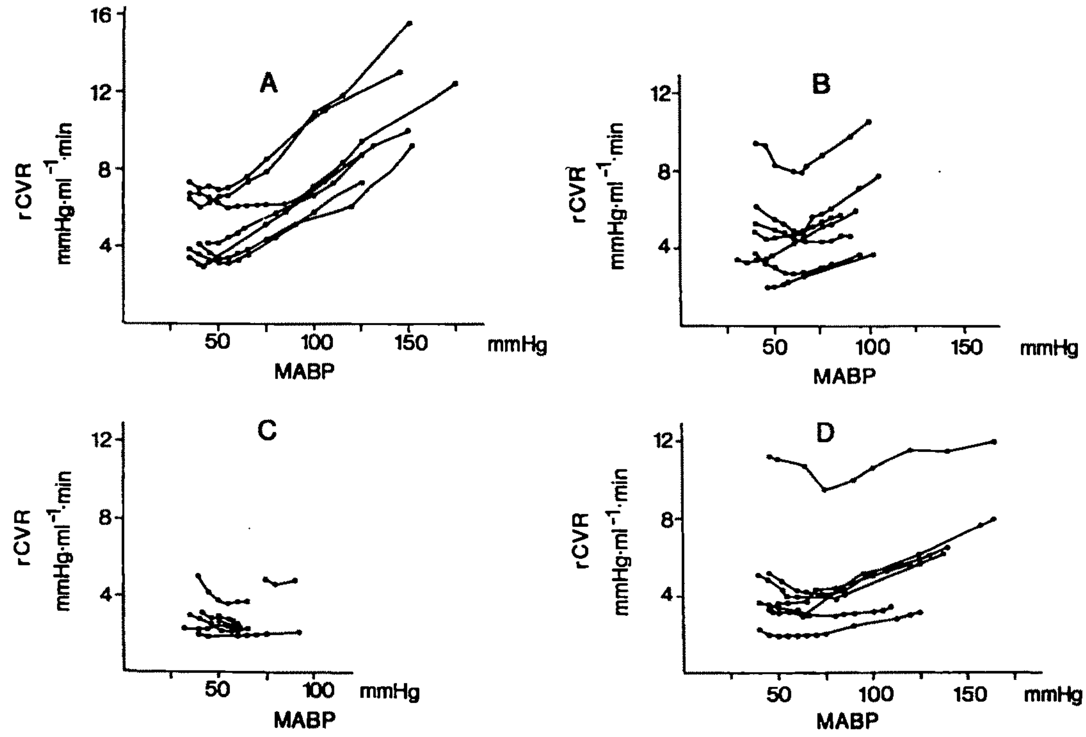

Figure 4. Illustrations of the regional vascular resistance (rCVR) in seven pigs during reduction of mean arterial blood pressure (MABP) by graded inhibition of venous return before hypotension (A) and during light (B) and moderate (C) hypotension induced by sodium nitroprusside. (D) The reaction 20–30 min after termination of the sodium nitroprusside infusion.

or the slight increase in rCBF found in the present study during SNP-induced moderate hypotension is not related to a preserved autoregulatory mechanism, but is rather due to a direct cerebral vasodilatory effect of SNP in parallel with the reduced perfusion pressure.

Cerebral autoregulation has not been studied during SNP-induced *slight* hypotension (MABP ≈ 90 mm Hg). The present study showed that angiotensin infusion may cause an increase in both rCBF and rCVR, whereas a blood pressure decrease (caval block) may cause a reduction of both the rCBF and the rCVR down to MABP levels of about 60 mm Hg. These findings indicate that the cerebral autoregulation was impaired, but not abolished as during moderate hypotension. Thus, the autoregulatory disturbance induced by SNP seems to be dose-dependent. Using the same experimental model, we have previously demonstrated a similar dose dependency during adenosine- and isoflurane-induced hypotension (13,14).

Cerebrovascular Effects After Hypotension

A marked posthypotensive increase in rCBF without hypertension was found. Such hyperemia, with or without rebound hypertension, has also been reported in clinical studies (2,4). This suggests a prolonged cerebral vasodilation after a restoration of normal systemic variables of SNP and agrees with the findings of Auer (28), who demonstrated persisting dilation of the canine pial vessels, mainly the smaller arterioles, after SNP infusion. In the present study, the marked vasodilation after SNP-induced hypotension could also be the result of cyanide formation from the high doses of SNP that were required for the hypotension. However, no signs of significant cyanide formation, such as metabolic acidosis or reduced cerebral oxygen uptake, were seen. The SNP treatment could be associated with an undetected cerebral extracellular fluid metabolic acidosis.

There was a marked difference in the autoregulatory response after SNP-induced hypotension depending on whether the MABP was increased or decreased. Although cerebral autoregulation during MABP decrease (caval block) was still impaired after 1 h (Figures 4 and 5), it had completely recovered already during MABP increase at the first posthypotensive challenge (angiotensin infusion, Figures 1 and 2). One explanation of this discrepancy may be that different-sized vessels are involved in the autoregulatory mechanism depending on the level of MABP and whether the blood pressure is increased or decreased. The autoregulatory response to hyper-

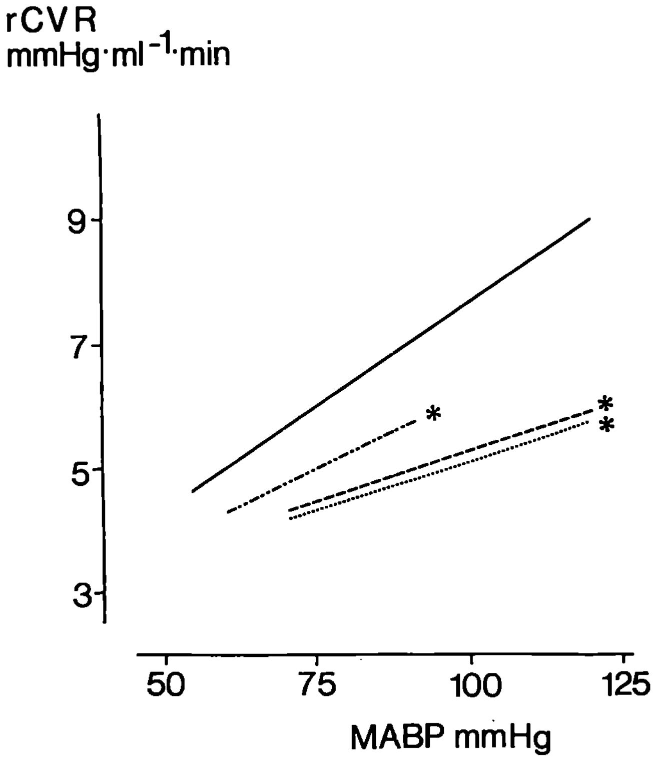

Figure 5. Regression lines (mean values of seven experiments) for the decrease in regional cerebral vascular resistance (rCVR) during reduction of mean arterial blood pressure (MABP) by graded inhibition of venous return (caval block), before, during, and after SNP infusion (see Methods). ——— control, _._._ light SNP-induced hypotension, ... 20–30 min after and ---- 45–65 min after SNP-induced hypotension. Cerebral vascular resistance was not affected during moderate hypotension (not illustrated in the figure). *$P < 0.05$, significant difference compared with the prehypotensive situation.

tension above 100 mm Hg has been suggested mainly to involve the larger surface vessels of the brain (17). These vessels may regain the ability to constrict, whereas the smaller arterioles, affected more by SNP (28), could still have been dilated when the hypertensive challenges were performed after SNP-induced hypotension. Our findings however, are in contrast to those of Keaney et al. (11), who found disturbed autoregulatory responses to increases in MABP up to 2 h after a 2-h hypotensive period in baboons. Furthermore, a similar disturbance was also found in cats immediately after SNP-induced hypotension with a duration of more than 4 min (12), and this disturbance was dependent on the duration of the SNP-induced hypotension and, consequently, the total dose.

The cerebrovascular autoregulatory responses during blood pressure reduction caused by hemorrhage involve both larger and smaller pial vessels down to an MABP of about 90 mm Hg (29), but below this level the dilation of the smaller vessels predominates (17,29). If SNP has a more prolonged effect in smaller than in larger vessels, as indicated above, this may explain why rCVR decreased only slightly more during caval block in the posthypotensive period. Even if the cerebral autoregulatory responses to decreases in blood pressure were markedly impaired during and after SNP-induced hypotension, it should be noted that at the lower limit of autoregulation in these situations, rCBF was considerably higher than before the administration of SNP (Table 3), indicating preserved cerebral perfusion.

It might be argued that the procedures with repetitive tests could themselves affect the cerebral autoregulatory response. One pig not included in this study and not given any hypotensive drug was subjected to four repetitive angiotensin tests and vena caval blocks over a 4-h period. This animal showed preserved autoregulation throughout the experiment. It is therefore suggested that the posthypotensive impairment of cerebral autoregulation found in the present study was caused by SNP administration rather than by a time-dependent phenomenon or by the repetitive tests. Furthermore, in two studies in pigs made hypotensive by adenosine (13) and isoflurane (14), the rCVR reactivity to caval block recovered within 40–60 and 25–50 min, respectively.

We conclude that CBF is maintained during SNP-induced hypotension in the pig to MABP levels of about 60 mm Hg owing to a direct vasodilatory effect of SNP and that the cerebral autoregulatory re-

Table 3. Mean Arterial Blood Pressure, Regional Cerebral Vascular Resistance, and Regional Cerebral Blood Flow at *the Lower Limit* of Autoregulation[a]

	I	II	III	IV	V
MABP (mm Hg)	54 ± 6	60 ± 5	—	70 ± 5[b]	70 ± 7[b]
rCVR (mm Hg·mL^{-1}·min)	4.7 ± 0.6	4.3 ± 0.7	2.7 ± 0.4[b]	4.1 ± 0.9	4.3 ± 1.4
rCBF (mL/min)	12.0 ± 1.4	15.3 ± 2.4	22.5 ± 2.6[b]	19.4 ± 2.6[b]	20.5 ± 3.9

MAPB, mean arterial blood pressure; rCVR, regional cerebral vascular resistance; rCBF, regional cerebral blood flow.
I–IV ($n = 7$), V ($n = 5$).

[a] Determined as the lowest regional cerebral vascular resistance during vena caval blockade before (I) and during slight (II) and moderate (III) hypotension induced by sodium nitroprusside as well as 20–30 min (IV) and 45–65 min (V) after hypotension.

[b] Significant difference ($P < 0.05$) compared with control.

sponses to both increases and decreases in MABP are impaired in a dose-dependent manner. After termination of SNP administration, the cerebral autoregulatory response to an increase in blood pressure is more rapidly recovered than the response to a decrease in blood pressure.

The authors thank Kerstin Librén and Britt Lingberth for their skillful technical assistance.

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Cerebral Autoregulation in Awake Versus Isoflurane-Anesthetized Rats

William E. Hoffman, PhD, Guy Edelman, MD, Eberhard Kochs, MD, Christian Werner, MD, Laurence Segil, MD, and Ronald F. Albrecht, MD

Anesthesiology Department, Michael Reese Hospital, University of Illinois, Chicago, Chicago, Illinois and Anesthesiology Department, University Hospital Eppendorf, Hamburg, Germany

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We evaluated regional cerebral and spinal cord blood flow in rats during isoflurane anesthesia. Tissue blood flow was measured in cerebral cortex, subcortex, midbrain, and spinal cord using radioactive microspheres. Blood flow autoregulation was measured within the following arterial blood pressure ranges (mm Hg): 1 = <50, 2 = 50–90, 3 = 90–130, 4 = 130–170, 5 = >170. Arterial blood pressure was increased using phenylephrine infusion and decreased with ganglionic blockade and hemorrhage. Three treatment groups were studied: 1 = awake control, 2 = 1.0 minimum alveolar anesthetic concentration (MAC) isoflurane, 3 = 2.0 MAC isoflurane. Autoregulation was seen in awake rats from 50 to 170 mm Hg in all tissues. The autoregulatory coefficient (change in blood flow/change in blood pressure) was increased in midbrain and spinal cord during 1.0 MAC isoflurane and in all tissues during 2.0 MAC isoflurane ($P < 0.05$). Within the arterial blood pressure range of 90–130 mm Hg, isoflurane produced the following changes in tissue blood flow (percent of awake control): 1.0 MAC isoflurane: cortex = 87% ± 8% ($P > 0.30$), subcortex = 124% ± 11% ($P > 0.05$), midbrain = 263% ± 20% ($P < 0.001$), spinal cord = 278% ± 19% ($P < 0.001$); 2.0 MAC isoflurane: cortex = 137% ± 13% ($P < 0.05$), subcortex = 272% ± 24% ($P < 0.001$), midbrain = 510% ± 53% ($P < 0.001$), spinal cord = 535% ± 50% ($P < 0.001$). These results show that isoflurane produces dose-dependent cerebral vasodilation and loss of autoregulation which is regionally specific.

(Anesth Analg 1991;73:753–7)

Previous studies indicate that isoflurane produces dose-related changes in cerebral autoregulation and regional cerebral blood flow (CBF). McPherson and Traystman (1) reported that in dogs cerebral autoregulation is maintained during administration of 1.4% isoflurane but not during 2.8% isoflurane. They did not report a difference in autoregulation between brain regions or spinal cord with isoflurane anesthesia. However, responses during isoflurane administration were not compared with a control treatment. Hansen et al. (2,3) reported that 1.0 minimum alveolar anesthetic concentration (MAC) halothane produced more vasodilation in cortex than 1.0 MAC isoflurane. In contrast, CBF increases more in subcortex than in cortex with increasing doses of isoflurane (4). These results suggest that there are regional differences in the cerebrovascular response to isoflurane. It is unclear whether isoflurane-induced cerebrovasodilation corresponds to regional changes in autoregulation. In this study we measured blood flow in cortex, subcortex, midbrain, and spinal cord of awake rats and rats anesthetized with 1.0 and 2.0 MAC isoflurane. Tissue blood flow was evaluated as a function of arterial blood pressure to compare changes in CBF and autoregulation.

Methods

Surgical Preparation

This study was approved by the Michael Reese Animal Care Committee. Thirty-seven Sprague-Dawley rats weighing 300–450 g were investigated. The rats were anesthetized with isoflurane in a bell jar and their tracheas were intubated. Ventilation was controlled with 2% isoflurane expired concentration in a 10:1 air/oxygen mixture using a small animal respirator. Both femoral arteries and one femoral vein were cannulated with polyethylene catheters filled with heparinized normal saline solution. These catheters were used for arterial blood pressure monitoring, blood withdrawal, and drug administration. A catheter was inserted into the left ventricle through the right common carotid artery for microsphere injec-

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Accepted for publication September 23, 1991.

Address correspondence to Dr. Hoffman, Anesthesiology Department, Michael Reese Hospital, Chicago, IL 60616.

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0003-2999/91/$3.50

tions. Placement was confirmed by observation of the left ventricular pressure pattern.

Treatment Groups

In awake rats (group 1, n = 14) catheters were tunneled subcutaneously and exited from a small incision in the back. All incisions were infiltrated with 0.25% bupivacaine and closed. The isoflurane was then discontinued and the trachea was extubated. After 2 h of recovery, the animals were tested in their home cage.

In rats anesthetized with 1.0 MAC isoflurane (group 2, n = 13), expired isoflurane was adjusted to 1.4% in room air using a Datex anesthetic agent monitor at the end of surgery (5). In group 3 (n = 10), expired isoflurane was adjusted to 2.8% isoflurane in room air. Isoflurane-anesthetized rats were allowed 30 min to adjust to the isoflurane concentration before the start of the study. Rectal and skull temperatures were measured using Yellow Springs thermistor probes and were maintained at 37°C using an overhead heat lamp. Arterial carbon dioxide tension ($Paco_2$) was maintained at 35–40 mm Hg by adjusting ventilation. Arterial pH (pHa) was adjusted with intravenous bicarbonate injections if necessary.

Cerebral Blood Flow Measurement

Mean arterial blood pressure was increased by intravenous infusion of phenylephrine (0.5 mg/mL) or decreased with trimethaphan (5 mg/mL) combined with blood withdrawal. The infusion rate for both drugs was less than 0.05 mL/min. Arterial blood pressure was stable for 5 min before each microsphere test. Blood pressures were increased or decreased randomly. An attempt was made to test each rat over as wide a mean arterial blood pressure range as possible. Fifteen-micron microspheres (New England Nuclear) were used with four different radioactive labels: ^{57}Co, ^{113}Sn, ^{46}Sc, and ^{85}Sr. Stock solutions containing 500,000 microspheres/mL were suspended in isotonic saline with 0.1% Tween 80. After vortexing the microsphere solution for 1 min, 0.2 mL (100,000 microspheres) was injected into the left ventricle through the ventricular catheter (dead space = 0.06 mL) and flushed with 0.2 mL of saline. Reference arterial blood samples were withdrawn from a femoral artery catheter at a rate of 0.4 mL/min using a Harvard infusion-withdrawal pump. Withdrawal was started immediately before each microsphere injection and continued for 45 s after the end of each injection. Ventricular pressure patterns were confirmed before each microsphere injection and blood pressure was monitored throughout the microsphere test to ensure constant pressure. Arterial oxygen tension (Pao_2), $Paco_2$, and pHa were evaluated for each CBF measurement using an IL 1303 blood-gas analyzer.

At the conclusion of the CBF measurements, the rat was killed by anesthetic overdose and the brain and spinal cord were removed. The brain was dissected into cortex, subcortex, and midbrain sections and weighed. Radioactivity of tissue samples and reference blood samples were analyzed using a Nuclear Chicago 1035 gamma counter and a Nuclear Data 600 multichannel analyzer. Cerebral blood flow was calculated using the following formula: CBF = (CT/CB) × (WR/TWT) × 100, where CBF is the tissue blood flow ($mL \cdot 100\ g^{-1} \cdot min^{-1}$), CT is the counts in the tissue, CB is the counts$\cdot mL^{-1} \cdot min^{-1}$ of reference arterial blood, WR is the withdrawal rate of reference arterial blood (mL/min), and TWT is the weight (g) of the tissue.

Both kidneys were also dissected out, weighed, and analyzed for radioactivity. A similar level of activity of each microsphere between left and right kidneys (<10% difference) was taken as an indication of adequate mixing of microspheres in the heart and an even distribution throughout the body.

Statistical Methods

All data are reported as mean ± SE. Cerebral blood flow measures were grouped within the following arterial blood pressure ranges (mm Hg): 1 = <50, 2 = 50–90, 3 = 90–130, 4 = 130–170, 5 = >170. Tissue blood flow was compared as a function of arterial blood pressure and anesthetic treatment using a two-way analysis of variance and Tukey's tests for post hoc comparisons. The autoregulatory coefficient and standard error of the coefficient were calculated using a least-squares fit for the change in blood flow over the change in arterial blood pressure within the blood pressure range of 50–170 mm Hg. Autoregulatory coefficients were compared between treatment groups using an analysis of covariance.

Results

Physiologic variables are shown in Table 1. $Paco_2$ and pHa were decreased with arterial blood pressures below 50 mm Hg, but there was no significant difference between treatment groups. $Paco_2$ was maintained between 31 and 40 mm Hg at higher blood pressures in all groups. Although there was no difference in $Paco_2$ between treatment groups, CO_2 tension was consistently 3–7 mm Hg lower in awake compared with isoflurane-anesthetized rats over the entire mean arterial blood pressure range.

In awake rats, autoregulation was seen between 50

Table 1. Mean Arterial Blood Pressure, Pa_{CO_2}, Pa_{O_2}, and pHa in Awake and Isoflurane-Anesthetized Rats

Treatment	MABP range (mm Hg)	*n*	MABP (mm Hg)	Pa_{CO_2} (mm Hg)	Pa_{O_2} (mm Hg)	pHa
Awake	<50	3	47 ± 2[a]	26.0 ± 1.0[a]	131 ± 8	7.42 ± 0.10
	50–90	9	71 ± 3[a]	31.1 ± 1.2	95 ± 6	7.47 ± 0.01
	90–130	13	116 ± 3	35.7 ± 0.6	97 ± 2	7.44 ± 0.01
	130–170	14	146 ± 3[a]	34.0 ± 0.9	91 ± 2	7.43 ± 0.01
	>170	6	192 ± 8[a]	31.6 ± 1.4	89 ± 2	7.41 ± 0.01
1.0 MAC isoflurane	<50	5	36 ± 5[a]	34.2 ± 4.0	94 ± 8	7.37 ± 0.04
	50–90	12	69 ± 3[a]	38.1 ± 0.7	91 ± 9	7.39 ± 0.01
	90–130	13	115 ± 3	38.8 ± 0.6	96 ± 8	7.40 ± 0.01
	130–170	7	139 ± 3[a]	40.7 ± 1.1	75 ± 9	7.38 ± 0.01
	>170	3	185 ± 9[a]	35.7 ± 2.1	61 ± 10	7.39 ± 0.02
2.0 MAC isoflurane	<50	5	38 ± 3[a]	39.6 ± 1.0	100 ± 4	7.29 ± 0.05
	50–90	7	69 ± 4[a]	40.8 ± 0.9	82 ± 3	7.39 ± 0.01
	90–130	10	110 ± 4	40.5 ± 0.8	93 ± 5	7.38 ± 0.01
	130–170	5	147 ± 5[a]	37.5 ± 1.8	102 ± 10	7.39 ± 0.02
	>170	3	190 ± 8[a]	34.5 ± 2.0	87 ± 10	7.34 ± 0.04

MABP, mean arterial blood pressure; Pa_{CO_2}, arterial carbon dioxide tension; Pa_{O_2}, arterial oxygen tension; pHa, arterial pH; MAC, minimum alveolar anesthetic concentration.

[a] $P < 0.05$ compared with mean arterial blood pressure range 90–130 mm Hg.

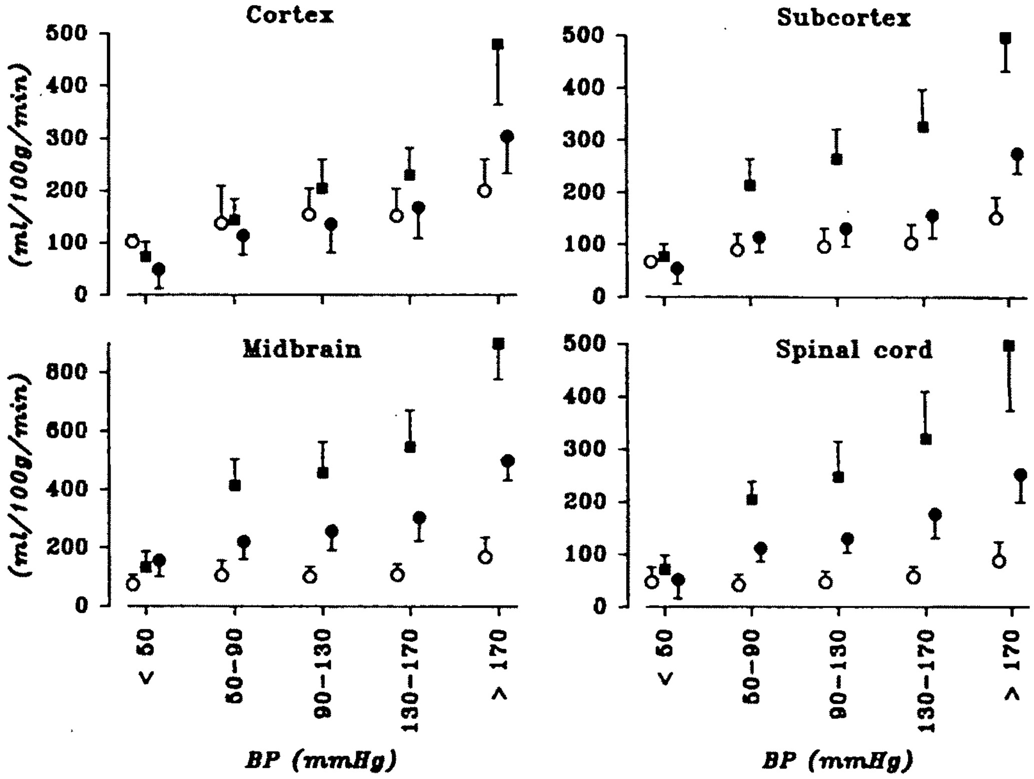

Figure 1. Regional blood flow in awake and isoflurane-anesthetized rats as a function of arterial blood pressure (BP). There was a significant effect of isoflurane treatment and blood pressure in all tissue regions ($P < 0.01$). ○, 0 MAC; ●, 1.0 MAC; ■, 2.0 MAC.

and 170 mm Hg in all tissues (Figure 1). The autoregulatory coefficient (change in blood flow/change in blood pressure) was significantly increased with 1.0 MAC isoflurane in midbrain and spinal cord and in all tissues with 2.0 MAC isoflurane (Table 2). Within the blood pressure range of 90–130 mm Hg, CBF was as follows ($mL \cdot 100\ g^{-1} \cdot min^{-1}$): awake control ($n = 15$): cortex = 159 ± 13, subcortex = 106 ± 8, midbrain = 97 ± 10, spinal cord = 51 ± 4; 1.0 MAC isoflurane ($n = 18$): cortex = 140 ± 13, subcortex = 132 ± 12, midbrain = 263 ± 20 ($P < 0.001$ compared with control), spinal cord = 142 ± 10 ($P < 0.001$);

Table 2. Autoregulatory Coefficient (Change in Blood Flow/Change in Arterial Blood Pressure) Within the Blood Pressure Range of 50–170 mm Hg

Tissue	Awake	1.0 MAC isoflurane	2.0 MAC isoflurane
Cortex	0.60 ± 0.39	1.35 ± 0.33	3.24 ± 0.67[a]
Subcortex	0.55 ± 0.25	1.10 ± 0.27	3.31 ± 0.57[a]
Midbrain	0.40 ± 0.35	2.31 ± 0.53[a]	6.38 ± 1.35[a]
Spinal cord	0.42 ± 0.15	1.33 ± 0.26[a]	3.90 ± 0.72[a]

MAC, minimum alveolar anesthetic concentration.
Data given as ± standard error of coefficient.
[a] $P < 0.05$ compared with awake value.

2.0 MAC isoflurane ($n = 12$): cortex = 220 ± 20 ($P < 0.05$), subcortex = 289 ± 26 ($P < 0.001$), midbrain = 495 ± 52 ($P < 0.001$), spinal cord = 273 ± 26 ($P < 0.001$).

Discussion

Our results show that in awake rats, cerebral autoregulation is maintained with arterial blood pressures between 50 and 170 mm Hg. This is consistent with previous reports (6–8). One MAC isoflurane did not significantly change autoregulation or CBF in cortex or subcortex compared with awake controls. This agrees with work in humans and animals (9–12). Midbrain and spinal cord showed significant increases in blood flow and attenuation of autoregulation during 1.0 MAC isoflurane. During 2.0 MAC isoflurane, blood flow was increased and autoregulation was attenuated in all tissues, with midbrain and spinal cord blood showing the largest change. This is consistent with reports that isoflurane produces less cerebral vasodilation in cortex and larger effects in subcortical and lower brain regions (2,4,9). Our results show that midbrain and spinal cord are most sensitive to the cerebral vascular effects of isoflurane. These tissues demonstrate a relation between isoflurane-induced vasodilation and loss of autoregulation.

Regional CBF has been measured by other investigators during isoflurane anesthesia. Compared with control treatments, 1.0 MAC isoflurane produces no significant change in cortex CBF in rats, rabbits, cats, or humans (2,9–11). Maekawa et al. (4) saw regionally specific increases in CBF in rats with increasing isoflurane concentration. With 2.0 MAC isoflurane, increases in CBF were greater in subcortical than in cortical regions. Also in rats, Hansen et al. (2) found more cerebral vasodilation in cortex with 1.0 MAC halothane compared with 1.0 MAC isoflurane. In a later study, Hansen et al. (3) measured regional cerebral glucose consumption (CMR_{gl}) during 1.0 MAC halothane and 1.0 MAC isoflurane and concluded that regional CBF was closely related to decreases in brain metabolism. This suggests that during 1.0 MAC isoflurane, regional cerebral vascular resistance is dependent on metabolic demand. However, with 2.0 MAC isoflurane, Maekawa et al. (4) saw a wide regional variation in CBF/CMR_{gl} ratios. They concluded that nonmetabolic regulatory mechanisms control regional CBF during high-dose isoflurane administration.

The association of increases in regional CBF with changes in autoregulation during isoflurane is unclear. During 1.0 MAC isoflurane, autoregulation is maintained (1,9). McPherson and Traystman (1) reported that midbrain and spinal cord autoregulation are intact in dogs during administration of 1.4% isoflurane. However, the response in these tissues was not compared with a control treatment. We found that midbrain and spinal cord autoregulation were present during 1.0 MAC isoflurane, but significant changes were seen compared with awake controls. These changes in autoregulation were consistent with increases in blood flow in midbrain and spinal cord during 1.0 MAC isoflurane. McPherson and Traystman (1) also reported that autoregulation was abolished in all brain regions and spinal cord during administration of 2.8% isoflurane. Our results agree with this conclusion. Midbrain tissue showed the greatest increase in blood flow during 2.0 MAC isoflurane and the greatest variation in blood flow in relation to blood pressure. It is unclear whether this represents a greater vasodilatory capability in midbrain or less responsiveness to isoflurane in other tissues. Although regional vascular differences in response to isoflurane are consistent in the rat (2,4), these effects may be species dependent (1).

It may be questioned whether phenylephrine and trimethaphan are appropriate drugs to test autoregulation. Strandgaard et al. (13) have shown that the sympathetic nervous system has little effect on the upper limit of autoregulation. Consistent with this, Sokrab and Johansson (14) reported that neither norepinephrine nor phenylephrine altered the upper limit of autoregulation in rats. In contrast, both cervical sympathectomy and α-adrenergic blockade extend the lower limit of autoregulation (15,16). This may be due to inhibition of sympathetic-induced vasoconstriction of large cerebral arteries when pial resistance vessels are maximally dilated (17,18). Trimethaphan inhibits cervical sympathetic activity and attenuates increases in catecholamines during hypotension but does not block the action of circulating adrenergic neurotransmitters at cerebrovascular receptors. Therefore, it is likely that cerebral resistance vessels showed normal reactivity at both the upper and lower limits of blood pressure measurement.

Another question is whether 5 min is an adequate period after a blood pressure change to measure autoregulation. Previous studies have shown that shifts in autoregulatory slopes related to arterial blood pressure are minimal after 5 min (19).

In these studies, $Paco_2$ was consistently lower (3–7 mm Hg) in awake compared with isoflurane-anesthetized rats. Previous reports indicate that a 1 mm Hg decrease in $Paco_2$ will decrease CBF by 2%–4% (20,21). This suggests that CBF may be 10%–20% lower than normal in awake rats because of hyperventilation. It is not expected that a slightly lower $Paco_2$ would affect regional difference in CBF or autoregulation.

In conclusion, we have shown that isoflurane produces dose-related increases in CBF and loss of autoregulation that are significant with 1.0 MAC isoflurane in midbrain and spinal cord and with 2.0 MAC isoflurane in cortex and subcortex. This indicates that lower brain regions are more sensitive to the vasoplegic effects of isoflurane. Differences in brain and spinal cord sensitivity to the vasodilatory and vasoplegic effects of isoflurane may be important in clinical cases of lower brain or spinal cord injury. In these cases, vasodilation produced by isoflurane may increase intracranial pressure and exacerbate ischemia. These conclusions cast doubt on the decision to use high-dose isoflurane in patients with spinal cord injury. It is expected that other inhaled anesthetics such as halothane would also abolish autoregulation in high concentrations, but may produce less cerebrovasodilation in spinal cord and lower brain regions compared with isoflurane (2,3). However, these comparisons have not been made.

We thank Susan Anderson for technical assistance and Lois Boler for preparation of the manuscript.

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Effects of Halothane in Low Concentrations on Cerebral Blood Flow, Cerebral Metabolism, and Cerebrovascular Autoregulation in the Baboon

Thomas Brüssel, Dr med, William Fitch, Prof PhD, FFARCS, Gerhard Brodner, Dr phil,
Irena Arendt, Dr med, and Hugo Van Aken, Prof Dr med

Klinik und Poliklinik für Anästhesiologie und Operative Intensivmedizin der Westfälischen Wilhelms-Universität, Münster, Germany; Department of Anaesthesia, University of Glasgow, Royal Infirmary, Glasgow, Scotland; and Department of Anesthesiology, University Hospital, Katholieke Universiteit Leuven, Leuven, Belgium

Halothane in anesthetic concentrations causes cerebral vasodilatation and decreases cerebral oxygen consumption ($CMRo_2$). The purpose of this study was to evaluate cerebral blood flow (CBF) and $CMRo_2$ changes associated with low concentrations of halothane. In eight normoventilated baboons with background anesthesia maintained with phencyclidine and nitrous oxide, CBF and $CMRo_2$ were studied during the administration of end-tidal concentrations of halothane (0.125, 0.25, 0.375, 0.5, 0.75, and 1.0 vol%). Arterial blood pressure was supported by an infusion of angiotension II amide at 0.75 and 1.0 vol% of halothane to maintain an adequate cerebral perfusion pressure. In addition, cerebrovascular autoregulation was tested before and during the administration of 0.375, 0.75, and 1.0 vol% of halothane. Cerebrovascular autoregulation was assessed by observing the response of CBF to an acute increase in mean arterial pressure produced by angiotensin. $CMRo_2$ decreased as the concentration of halothane was increased. At low halothane concentrations (0.125–0.375 vol%), CBF decreased; however, at concentrations above 0.375 vol%, CBF increased with a decrease in cerebrovascular resistance. Autoregulation was intact during 0.375 vol% of halothane, but with 0.75 and 1.0 vol% of halothane, CBF was passively dependent on cerebral perfusion pressure, suggesting impaired autoregulation.

(Anesth Analg 1991;73:758–64)

In anesthetic concentrations, halothane (1–9), enflurane (10–13), and isoflurane (8–11,14–16) decrease the cerebral metabolic oxygen consumption rate ($CMRo_2$); yet they cause dilatation in the cerebral vascular bed and consequently, an increase in cerebral blood flow (CBF). The reason for this dissociation of CBF from $CMRo_2$ is not known, although Ramani et al. (17) suggest the influence of some neurogenic or chemical mediator. Although halothane, enflurane, and isoflurane show a similar overall pattern of alterations on CBF and $CMRo_2$, they differ in the magnitude of induced changes. At similar alveolar concentrations, halothane is associated with the largest increase in CBF (8,9,11,13,14,18), whereas isoflurane causes the largest decrease in $CMRo_2$ with only small changes in CBF (8,9,11,13). However, Drummond and Todd (19) report similar values of CBF associated with equal minimal alveolar concentrations of halothane and isoflurane in the normocapnic cat. In an earlier study, we found a biphasic response of CBF with increasing concentrations of isoflurane (16). Low concentrations (up to 0.5 ± 0.35 vol%) produced a decrease in CBF concomitant with a decrease in $CMRo_2$. At higher concentrations, the relation between blood flow and metabolism was altered, leading to an increase in blood flow despite a further decrease in metabolism. The purpose of this study was to evaluate the effects of low concentrations of halothane on CBF, $CMRo_2$, and cerebrovascular autoregulation. The study was approved by the authors' institutional animal investigation committee. The experiments were performed according to our institution's standards for laboratory animal care.

This study was performed at the Wellcome Surgical Institute, the University of Glasgow and was presented in part at the annual meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 1990.

The financial assistance for this study received from Deutsche Abbott GmbH is acknowledged with gratitude.

Accepted for publication August 26, 1991.

Address correspondence to Dr. Brüssel, Klinik und Poliklinik für Anästhesiologie und Operative Intensivmedizin, Westfälische Wilhelms-Universität, Albert-Schweitzer Strasse 33, 4400 Münster, Germany.

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0003-2999/91/$3.50

Methods

Eight male baboons (9.0–12.5 kg) were premedicated with phencyclidine, 12 mg IM. Anesthesia was induced with thiopental, 7.5 mg/kg IV. Muscle relaxation was achieved with succinylcholine, 20 mg IV. After tracheal intubation, the animals were mechanically ventilated with 67% nitrous oxide in oxygen. In addition, anesthesia was maintained by a continuous IV infusion of phencyclidine, $0.15\ \mathrm{mg \cdot kg^{-1} \cdot min^{-1}}$. To aid ventilation, succinylcholine (50 mg IM) was administered every 30 min. Ventilation was adjusted to maintain arterial carbon dioxide tension between 38 and 42 mm Hg. End-tidal carbon dioxide concentrations were measured continuously with an infrared carbon dioxide analyzer. The body temperature of the animals was kept between 36 and 37°C by means of heating lamps. Cannulas were placed in the abdominal aorta (via femoral artery) for the measurement of arterial blood pressure and in the left femoral vein for the infusion of intravenous anesthesia and additional fluids. A balloon-tipped, flow-directed pulmonary artery occlusion catheter was placed in the pulmonary artery via the right femoral vein. A catheter was placed into the superior sagittal sinus for the measurement of sagittal sinus venous pressure (SSVP) and for the collection of cerebral venous blood. Another catheter was placed subdurally to monitor intracranial pressure (ICP). The right common carotid artery and its branches were exposed by blunt dissection. A catheter was placed in the linguofacial trunk of the external carotid artery and all other branches of the external carotid artery were ligated distally. This catheter was used for the injection of ^{133}Xe into the internal carotid artery to determine CBF. After the removal of the scalp and right temporal muscle, a scintillation crystal was placed over the exposed skull. The crystal was arranged in a way that prohibited the counting of radioactivity from surrounding tissue.

Heart rate, arterial pressure, right atrial pressure, pulmonary artery pressure, SSVP, and ICP were monitored continuously (Gould Statham P23 ID transducers). The level of the external auditory meatus was considered the zero reference level. Systemic vascular resistance, cerebral perfusion pressure, and cerebral vascular resistance (CVR) were calculated using standard formulas.

$\mathrm{CMRO_2}$ was determined as

$$\mathrm{CBF} \times (\mathrm{CaO_2} - \mathrm{CvO_2}),$$

where $\mathrm{CaO_2}$ is the cerebral arterial oxygen content and $\mathrm{CvO_2}$ is the cerebral venous oxygen content.

Pulmonary capillary wedge pressure and cardiac output (CO) were obtained when indicated. Cardiac output was measured in duplicate by the thermodilution technique using 2 mL of cold 5% dextrose (Cardiac Output Computer, 9510, Edwards Laboratories). Mean pressures were calculated by adding one-third of the pulse pressure to the diastolic pressure:

$$\mathrm{MAP} = \frac{1}{3}(\mathrm{SAP} - \mathrm{DAP}) + \mathrm{DAP},$$

where MAP is the mean arterial blood pressure, SAP is the systolic arterial blood pressure, and DAP is the diastolic arterial blood pressure. After the injection of approximately 0.4–0.7 mCi ^{133}Xe (via the right lingual artery catheter), a washout curve was recorded over the right parietal area. Mean CBF was calculated from this curve by the height-area equation (20). With each determination of CBF, the oxygen content of arterial and cerebral venous blood was assessed (Lex-O-Con Oxygen Analyzer, Albury Instruments Ltd.). After the preparation, a 3-h stabilization period was allowed before baseline values were obtained. Halothane was administered stepwise in progressive increasing concentrations (0.125, 0.25, 0.375, 0.5, 0.75, and 1.0 vol%). End-tidal halothane concentrations were determined with an anesthetic monitor (Normac, Datex). After each desired end-tidal halothane concentration was reached, 10 min were allowed for systemic and cerebrovascular variables to stabilize. Then CBF was determined and all other variables were obtained. With each CBF determination samples of sagittal sinus venous blood were drawn in appropriate gas-tight glass syringes for the gas chromatographic determination of blood halothane concentration. In addition, in six of the eight animals arterial blood pressure was supported at 0.75 and 1.0 vol% of halothane to values above 70 mm Hg (above the lower limit of cerebral autoregulation) by a continuous infusion of angiotensin II amide (CIBA).

Cerebrovascular autoregulation was tested before the administration of halothane and in association with the administration of 0.375, 0.75, and 1.0 vol% of halothane. Autoregulation was assessed by observing the response of CBF to a sudden increase in MAP of approximately 20 mm Hg. The increase in MAP was produced by the infusion of angiotensin II amide.

Simple correlation coefficients between end-tidal and plasma halothane concentrations were obtained for each individual animal. Fisher's z-transformation was used to determine whether the population correlation coefficients were equal. If this was the case, a common correlation coefficient (r_w) was calculated.

Mean values and the standard deviation were calculated for each measurement. Statistical analysis was performed using an analysis of variance for repeated measures. In case of significant F values, polynomial contrasts were used to determine the shape of the curve that fitted the obtained data best. To find where the significant differences existed, a post hoc test of the successive differences and the differences to baseline, but not of all possible contrasts, was added to avoid a type I error. The probability of $P < 0.05$ was considered statistically significant.

Results

The plasma concentrations of halothane in the sagittal sinus venous blood and the corresponding end-tidal concentrations of halothane are shown in Table 1. Statistical analysis indicated a close correlation of end-tidal and plasma halothane concentrations for the individual animals. These correlation coefficients proved to be equal for the population. The weighted correlation coefficient showed that a close correlation existed between these measurements for the whole population with $r_w = 0.89$.

Effects on the Systemic Circulation

The administration of halothane in increasing concentrations was associated with linear dose-related decreases in MAP from 105 ± 12 mm Hg (baseline) to 48 ± 3 mm Hg (1.0 vol% of halothane), representing a 54.3% decrease in MAP at the highest halothane concentration ($P < 0.05$) (Table 2). A significant decrease in CO compared with the baseline value was observed at 1.0 vol% of halothane. Systemic vascular resistance decreased in a dose-related manner ($P < 0.05$). This decrease became significant compared with baseline at 0.375 vol% of halothane. Heart rate, right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure did not change during the entire experiment. The significant decrease in MAP was caused by a reduction in CO in combination with a reduction in SVR. Arterial hemoglobin concentrations and the hematocrits remained stable throughout the study.

Table 1. End-Tidal Halothane Concentrations and Corresponding Halothane Plasma Concentrations

End-tidal halothane concentration (vol%)	Plasma halothane concentration (mg/100 mL)
Baseline	Not detected
0.125	0.62 ± 0.26
0.25	1.23 ± 0.84
0.375	1.86 ± 0.8
0.5	2.63 ± 1.0
0.75	3.68 ± 1.42
1.0	5.10 ± 2.31

Values are mean ± SD.
$r_w = 0.89$.

Effects on Cerebrovascular Variables and Cerebral Metabolism

The baseline values of CBF and $CMRo_2$ were comparable to those obtained in previous studies using the same animal model and background anesthesia (16,21,22). Halothane, in increasing concentrations, was associated with a decrease in $CMRo_2$ from 3.4 ± 0.8 to 2.4 ± 0.4 mL $O_2 \cdot 100\ g^{-1} \cdot min^{-1}$ (Figure 1, Table 3) ($P < 0.05$). Statistical analysis showed that this decrease in $CMRo_2$ became significant compared with baseline with 0.25 vol% and the higher halothane concentrations. The course of the polynomial contrasts indicated a highly significant linear trend.

This linear decrease in cerebral metabolism was paralleled by a significant reduction (30.1%) in CBF from 55.8 ± 8.0 mL·100 $g^{-1} \cdot min^{-1}$ at baseline to 39.0 ± 4.0 mL·100 $g^{-1} \cdot min^{-1}$ at 0.375 vol% of halothane. The decrease in CBF was associated with an increase in CVR ($P < 0.05$). However, with 0.5 vol% of halothane CBF increased to 44.6 ± 9.5 mL·100 $g^{-1} \cdot min^{-1}$. With 0.75 and 1.0 vol% of halothane, CBF remained unchanged compared with 0.5 vol% of halothane. However, calculated CVR decreased significantly compared with the value at 0.375 vol% of halothane. If MAP was supported by the infusion of angiotensin II amide so as to achieve values within the autoregulatory range during the administration of 0.75 and 1.0 vol% of halothane, CBF increased further and was 12.9% above baseline with 1.0 vol% of halothane (Figure 1). The analysis of the polynomial contrasts for CBF showed a highly significant squared trend confirming the biphasic CBF response to increasing concentrations of halothane.

Intracranial pressure and SSVP remained unchanged at all halothane concentrations. Figure 2 shows the effect of an acute increase in MAP on CBF (changes in CBF are presented as ΔCBF). A 20-mm Hg increase in MAP before and during 0.375 vol% of halothane did not alter CBF. During 0.75 and 1.0 vol% of halothane, similar increases in MAP caused significant increases in CBF.

Discussion

The present data were obtained in baboons subjected to background anesthesia maintained with phencyclidine and nitrous oxide. Nitrous oxide was used to ensure that an adequate level of anesthesia was obtained without the addition of a volatile anesthetic

Table 2. Effects of Halothane in Increasing Concentrations on the Systemic Circulation

	Halothane (vol%)								
	Baseline	0.125	0.25	0.375	0.5	0.75	BP support 0.75	1.0	BP support 1.0
MAP (mm Hg)	105 ± 12	101 ± 10	91 ± 9[a]	85 ± 11[a]	77 ± 9[a]	67 ± 9[a]	82 ± 11	48 ± 3[a]	73 ± 6[a]
HR (beats)	109 ± 17	114 ± 22	114 ± 25	115 ± 26	113 ± 26	116 ± 25	110 ± 20	116 ± 20	114 ± 15
CO (L/min)	1.6 ± 04	1.6 ± 0.3	1.6 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.2	1.6 ± 0.3	1.2 ± 0.2[a]	1.4 ± 0.4
RAP (mm Hg)	4 ± 2	4 ± 2	4 ± 2	4 ± 2	4 ± 2	5 ± 2	5 ± 3	4 ± 1	5 ± 2
PAP (mm Hg)	18 ± 3	19 ± 4	18 ± 3	18 ± 3	18 ± 3	17 ± 3	18 ± 3	15 ± 4	19 ± 5
PCWP (mm Hg)	8 ± 3	8 ± 3	8 ± 3	8 ± 4	7 ± 3	7 ± 3	6 ± 2	7 ± 3	9 ± 3
SVR (dyne·s·cm^{-5})	5650 ± 662	5139 ± 963	4694 ± 967	4515 ± 972[a]	4282 ± 986[a]	3700 ± 897[a]	4652 ± 1032[a]	2999 ± 746[a]	4306 ± 869[a]

MAP, mean arterial blood pressure; HR, heart rate; CO, cardiac output; RAP, mean right atrial pressure; PAP, mean pulmonary artery pressure; PCWP, mean pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

$n = 8$; with BP support, $n = 6$.

Values are mean ± SD.

[a] $P < 0.05$ significant compared to baseline.

in this primate model. Although nitrous oxide is associated with an increase in CBF (9,23–28) and some conflicting reports exist about the effect of phencyclidine (21,29,30) on cerebral circulation and cerebral metabolism, the combination of these drugs as background anesthetics provides stable cerebrovascular variables in this experimental model (21,31). Therefore, the changes observed in this study are most likely to be the result of the added halothane. However, some influence of these other drugs on the changes associated with halothane cannot be excluded totally (9,32,33).

Angiotensin II amide, used to acutely increase or support arterial blood pressure when necessary, had no effect on the cerebral vasculature in the present animal model (16,21,22).

After instrumentation and time for stabilization, the protocol required an actual experimental period of several hours. In prior studies Strandgaard et al. (22) and Fitch et al. (21,31) demonstrated that time, per se, did not affect cerebrovascular and hemodynamic conditions in this model.

After each desired end-tidal halothane concentration was reached, 10 min was allowed for stabilization before the determination of CBF. We believed that a longer equilibration period might have interfered with the results. Albrecht et al. (7) observed that the CBF changes associated with halothane had the tendency to return to control values after 30 min. Therefore, if time would have had an effect on the results, it most likely would mean that the observed changes were attenuated by time and that the actual effect might even be more pronounced.

Halothane was administered purposely in increasing concentrations. Randomization of the sequence in which different concentrations of halothane were administered was not performed as this might have jeopardized the results. Halothane (0.75 and 1.0 vol%) impairs cerebrovascular autoregulation (6,8). Even halothane concentrations as little as 0.5 vol% might alter autoregulation (5). The impairment of

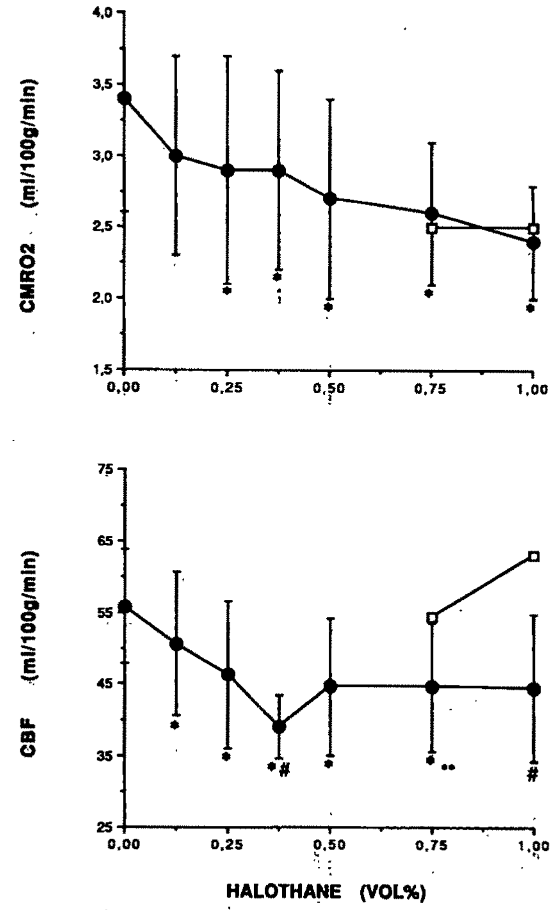

Figure 1. Alterations in cerebral metabolic rate for oxygen ($CMRo_2$) and cerebral blood flow (CBF) associated with increasing concentrations of halothane (-●-), (with blood pressure [BP] support -□-). ($n = 8$; with BP support, $n = 6$. Values are mean ± SD. $P < 0.05$ [*compared to baseline, #compared to previous value, **compared to CBF at 0.375 vol% of halothane.])

Table 3. Effects of Halothane in Increasing Concentrations on Cerebrovascular Parameters and Cerebral Metabolism

	Halothane (vol%)								
	Baseline	0.125	0.25	0.375	0.5	0.75	BP support 0.75	1.0	BP support 1.0
CBF (mL·100 g^{-1}·min^{-1})	55.8 ± 8.0	50.6 ± 10.0^{a}	46.3 ± 10.2^{a}	39.0 ± 4.0^{a,b}	44.6 ± 9.5^{a}	44.6 ± 9.0^{a,c}	54.4 ± 8.6^{b,c}	44.5 ± 10.2^{b}	63.0 ± 10.7^{b,c}
$CMRo_2$ (mL O_2·100 g^{-1}·min^{-1})	3.4 ± 0.8	3.0 ± 0.7	2.9 ± 0.8^{a}	2.9 ± 0.8^{a}	2.7 ± 0.7^{a}	2.6 ± 0.5^{a}	2.5 ± 0.4^{a}	2.4 ± 0.4^{a}	2.6 ± 0.5^{a}
AVo_2 (mL O_2·100 mL^{-1})	6.1 ± 1.2	5.9 ± 0.9	6.3 ± 1.1	7.3 ± 1.4^{a}	6.1 ± 0.7	5.8 ± 0.9	4.6 ± 0.7^{a,b}	5.4 ± 0.9^{b}	4.1 ± 1.0^{a,b}
CPP (mm Hg)	92 ± 10	89 ± 9	80 ± 6	74 ± 8	65 ± 7^{a}	55 ± 7^{a}	67 ± 5^{a}	35 ± 4	58 ± 7^{a}
ICP (mm Hg)	12 ± 2	12 ± 3	12 ± 3	11 ± 3	11 ± 2	12 ± 3	14 ± 5	12 ± 2	15 ± 4
SSVP (mm Hg)	13 ± 3	11 ± 3	11 ± 3	11 ± 3	11 ± 3	12 ± 3	15 ± 5	12 ± 2	15 ± 5
CVR (dyne·s·cm^{-5})	1.7 ± 0.1	1.8 ± 0.2	1.8 ± 0.3	2.0 ± 0.2^{a}	1.5 ± 0.3^{b}	1.3 ± 0.2^{a,c}	1.3 ± 0.2^{a,c}	0.8 ± 0.2^{a,b,c}	0.9 ± 0.2^{a,c}

CBF, cerebral blood flow; $CMRo_2$, cerebral metabolic rate for oxygen; AVo_2, cerebral arterial-venous oxygen content; CPP, cerebral perfusion pressure; ICP, intracranial pressure, SSVP, sagittal sinus venous pressure; CVR, cerebral vascular resistance; BP, blood pressure.

n = 8; with BP support, *n* = 6.

Values are mean ± SD.

$P < 0.05$ (^{a}significant compared to baseline, ^{b}compared to previous value, ^{c}compared to value at 0.375 vol% of halothane).

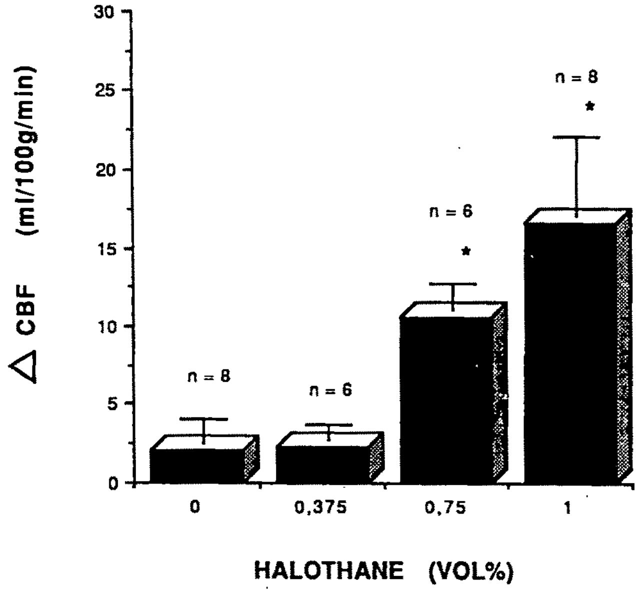

Figure 2. Change in cerebral blood flow (ΔCBF) associated with an acute increase in mean arterial blood pressure before halothane and during 0.375, 0.75, and 1.0 vol% of halothane. (Mean ± SD, $^{*}P < 0.05$.)

autoregulation will render the CBF dependent on systemic blood pressure and might alter the cerebral blood flow/cerebral metabolism relationship. How long such halothane-induced impairment of cerebrovascular autoregulation persists is not known.

Halothane caused a dose-dependent decrease in MAP. Although this reduction was expected, we did not intend to support arterial blood pressure, because we wanted to be able to compare the halothane results with those obtained for isoflurane in a previous study (16). However, the results of the first animals showed that at 0.75 and 1.0 vol% of halothane MAP had decreased by 36.2% and 54.3%, respectively. We believed that such a reduction in MAP might impair perfusion and the measured CBF would more likely reflect the overall hemodynamic state than the cerebrovascular condition. In the following six animals, arterial blood pressure was supported to values above the normal lower limit of autoregulation (65 mm Hg for hemorrhagic hypotension, 45 mm Hg for drug-induced hypotension in this baboon model [21]). Arterial blood pressure support at lower halothane concentrations was not performed, as with these concentrations cerebrovascular autoregulation was intact and CPP was within normal limits. Therefore, the decrease in MAP should not have altered CBF. If it had any effect on the cerebral vasculature, decreased MAP should have caused a further vasodilatation in addition to the direct vasodilating effect of halothane on cerebral vessels. However, even such an additional vasodilation was overcome by the vasoconstrictive effect of the $CMRo_2$ reduction.

The finding of this study, a decrease in CBF concomitant with a decrease in $CMRo_2$, is most likely the result of the decrease in cerebral function and oxygen demand. This suggests that, in the presence of phencyclidine and nitrous oxide, halothane in concentrations up to 0.375 vol% does not interfere with the physiologic metabolism-flow relationship. Cerebral blood flow decreased as a consequence of the decrease in $CMRo_2$. With halothane concentrations above 0.375 vol%, cerebral metabolism decreased further. The alterations in CBF were more variable. An increase in CBF with 0.5 vol% of halothane was followed by similar CBF values with 0.75 and 1.0 vol% of halothane in those animals in which blood pressure was allowed to decrease further. This pattern appeared to be due to low cerebral perfusion pressure (53 ± 7 and 35 ± 4 mm Hg, respectively) and impaired cerebral autoregulation, rather than vasoconstriction. When the cerebral perfusion pressure was kept above 55 mm Hg at the higher halothane concentrations (by arterial blood pressure support), a further increase in CBF was observed. Calculated CVR showed a significant decrease compared with the value at 0.375 vol% halothane. This finding suggests a biphasic response of CBF to increasing concentrations of halothane. Low concentrations decrease CBF parallel to the decrease in $CMRo_2$, whereas with halothane concentrations above 0.375 vol% CBF increases. This increase in CBF despite further decrease in $CMRo_2$ indicates an alteration of the relationship between blood flow and metabolism.

A comparison of the present findings with those reported by other investigators is difficult. Variations may be due to species differences, experimental design, instrumentation, and concomitant drug therapy. It is generally accepted that halothane causes a decrease in $CMRo_2$ and with concentrations above 1.0 MAC increases CBF. The reported changes in CBF associated with halothane in low concentrations are conflicting. In early publications, McDowall et al. (34,35) describe a decrease in CBF with 0.5 vol% of halothane. Similar findings were observed by Fitch et al. (21), Harp et al. (36), DeValois and Peperkamp (37), and Morita et al. (6). However, Theye and Michenfelder (4) and Todd et al. (8,11) demonstrated an increase in CBF of 20%–25% with 0.5 vol% of halothane. The change from decrease to increase in CBF that occurred between 0.375 and 0.5 vol% of halothane in the present study may explain the controversial reports. The concentration, where such a shift in pattern occurs, may vary slightly with different experimental protocols and animal species.

The biphasic pattern of CBF changes can be explained. At low concentrations of halothane, the reduction in CBF is probably not caused by a direct constrictive action of halothane on the vasculature, but originates from the reduction in $CMRo_2$ that causes vasoconstriction. At low halothane concentrations, this vasoconstrictive effect is more potent than the vasodilating property of halothane. However, at higher halothane concentrations (>0.375 vol%) the direct vasodilating effect overcomes this vasoconstrictive action and results in a net increase in CBF. Morita et al. (6) suggested such a biphasic pattern of CBF changes associated with halothane, but could not demonstrate it clearly as only one low concentration (0.5 vol%) was studied. Stullken et al. (38) reported an increase in CBF with halothane at low concentrations, but the measured CBF values were not compared with the baseline CBF but to an assumed lower level. In their experimental model, time by itself altered CBF. Compared with baseline, CBF decreased with concentrations up to 0.6 vol% of halothane in Stullken's experiments.

A similar biphasic pattern associated with the administration of anesthetic agents was observed for ether and cyclopropane (39) and methoxyflurane (35). The results presented by Van Aken et al. (16) in the same animal model as used in the present study indicate a similar pattern of CBF changes for isoflurane. The change from decreasing to increasing CBF with increasing concentrations of isoflurane occurred between 0.5 and 0.95 vol% of isoflurane (0.4–0.7 MAC). This is in the same range (0.4–0.5 MAC) where the change in the CBF flow pattern was observed in the present study (1 MAC halothane is approximately 1.0 vol% in the monkey [40]).

Cerebrovascular autoregulation was intact with low levels of halothane (0.125–0.375 vol%). At concentrations greater than 0.5 vol% of halothane, autoregulation was impaired and an acute increase in MAP was followed by a sudden increase in CBF.

The observed impairment of autoregulation with halothane at 0.75 and 1.0 vol% is in close agreement with the results reported by Miletich et al. (5), Morita et al. (6), and Todd and Drummond (8). In addition, Morita et al. observed an intact autoregulation with 0.5 vol% of halothane in nitrous oxide in the monkey (6). However, Miletich et al. report that cerebrovascular autoregulation is partially impaired with 0.5 MAC of halothane in their goat model (5).

The absence of an increase in ICP and SSVP despite an increase in CBF is somewhat surprising. However, a similar lack of ICP increase associated with an increase in CBF is reported by Drummond and Todd (19) for halothane and isoflurane. The present experiments were performed with young adult baboons. The stability of ICP may be attributed to the high cerebral compliance in these animals without intracranial pathology.

In conclusion, the general pattern of observed changes in cerebrovascular variables and cerebral metabolism associated with increasing low concentrations of halothane suggest that halothane does not differ basically from isoflurane, methoxyflurane, ether, or cyclopropane. However, the magnitude of induced CBF and $CMRo_2$ changes varies with the different agents. Each of these volatile anesthetics appears to decrease cerebral metabolism. In addition, the present data and the reports in the literature suggest that these anesthetics do not differ in regard to their general influence on CBF. Low concentrations cause a reduction in CBF, whereas higher concentrations lead to vasodilatation and a resulting increase in CBF.

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Valsalva Maneuver in Obstetrics: The Influence of Peripheral Circulatory Changes on Function of the Pulse Oximeter

Andrew M. Woods, MD, Jeffrey S. Queen, MD, and Dan Lawson, MD
Department of Anesthesiology, University of Virginia Health Sciences Center, Charlottesville, Virginia

Strenuous expulsive efforts involving sequential Valsalva maneuvers may result in maternal hypoxemia during the second stage of labor. Pulse oximetry has been used to assess oxygen saturation in laboring parturients, and this study was undertaken to evaluate the performance of the pulse oximeter (Nellcor) during the Valsalva maneuver. In both pregnant patients and nonpregnant volunteers, there were consistent interruptions in the transmission of oxygen saturation data during the Valsalva maneuver. To determine the physiologic events associated with this monitoring interruption, occlusive venous impedance plethysmographs and pulse volume amplitude recordings were obtained in volunteers performing the Valsalva maneuver. A marked decrease in pulse volume amplitude was noted, which adversely affected the oximeter's ability to distinguish physiologic arterial pulsations from background noise. Each Valsalva maneuver was associated with abrupt and transient changes in peripheral vascular volumes, thus presenting the oximeter with a rapidly changing signal for analysis that violated predetermined software criteria for pulse uniformity and caused an interruption in data transmission. The authors conclude that the Valsalva maneuver interferes with the ability of pulse oximeter technology to provide useful oxygen saturation data.

(Anesth Analg 1991;73:765–71)

Maternal and fetal hypoxemia may occur during the latter stages of labor in association with maternal respiratory abnormalities caused by pain and expulsive efforts (1). Continuous pulse oximetry has been used to monitor maternal blood oxygen saturation during parturition (2). However, in our use of the Nellcor pulse oximeter in parturients, the display of oxygen saturation data and maternal heart rate is repeatedly interrupted during maternal expulsive efforts. Because the interruptions occur during periods of sequential Valsalva maneuvers ("pushing") in the second stage of labor, peripheral vascular perturbations associated with the Valsalva maneuver and their interactions with the pulse oximeter were investigated in a series of experiments.

The technical foundation for modern pulse oximetry rests on the collection of concurrent pulse plethysmograph and colorimetric absorption data from tissue within the path of two light-emitting diodes and associated photodetectors. The absorption of two wavelengths of light (red [660 nm] and infrared [940 nm]) by blood pigments forms the basis for oxygen saturation determinations; the variation in infrared (IR) absorbance by a fluctuating volume of blood is the source of plethysmographic information. The software controlling the Nellcor oximeter is designed to compare many aspects of five consecutive pulse waveforms before oxygen saturation and pulse rate data are released to the front panel. For example, the absorbance fluctuations must be of sufficient amplitude to distinguish true pulsations from variations in background absorption (noise), the pulse data must be uniform across the five beats, and adequate color information must be present so that the Beer-Lambert law can be applied to estimate the concentrations of saturated and unsaturated hemoglobin. With each subsequent pulse, the first pulse of the five beat series is discarded and the newest beat is added and evaluated; the updated data are then reported on the oximeter front panel (3,4; Reid K, Nellcor Inc., personal communication).

If the newest pulse is rejected or not detected by the oximeter software, the oximeter cycles through a

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This study was supported in part by an equipment grant from Nellcor Inc., Haywood, Calif.

Portions of this paper were presented in abstract form at the International Anesthesia Research Society Meeting, Honolulu, Hawaii, February 1990.

Accepted for publication July 17, 1991.

Address correspondence to Dr. Woods, Department of Anesthesiology, University of Virginia Health Sciences Center, Box 238, Charlottesville, VA 22908.

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0003-2999/91/$3.50

complex set of hardware and software maneuvers designed to optimize pulse signal quality: this is designated by the manufacturer as the PTO (pulse time-out) mode (Reid K, personal communication). During this time the bouncing dot display is arrested and the front panel continues to display the data that were present at the time of the pulse rejection. Once an acceptable pulse is acquired, the bouncing dot display is activated; however, five heartbeats must be processed before new data are released by the oximeter. If no acceptable pulse waveform is detected for 10 s during the PTO mode, the machine enters the pulse search mode; the front panels revert to zero and the "pulse search" light is illuminated. The pulse search mode is also entered when the machine is first turned on. The resetting of signal acquisition variables in response to changes in the pulse quality is a designed task for the oximeter; however, "normal oximeter function" as used in this paper is defined as the typical display of valid heart rate and oxygen saturation data.

In the Nellcor N-100 oximeter, pulse wave morphology optimization is accomplished by software-directed changes in IR signal acquisition. However, concurrent changes in red signal strength may interfere with pulse wave identification. In the N-200 oximeter, these functions are independently controlled; theoretically, this should result in improved pulse wave analysis during poor pulsatile states (Reid K, personal communication).

Methods

This study was approved by the institutional human investigation committee. Subjects had no known physiologic abnormalities other than pregnancy, were not receiving any medications, and provided informed consent before participating in the study.

Pulse oximeter performance, with regard to the occurrence of the PTO mode in relation to the Valsalva maneuver, was studied in pregnant patients. To confirm that the effects of the Valsalva maneuver on oximetry were independent of factors associated with the pregnant state, similar experiments were performed in nonpregnant volunteers. In addition, the peripheral circulatory alterations associated with the Valsalva maneuver and their effects on oximeter function were studied in nonpregnant volunteers using noninvasive, calibrated peripheral vascular measurement techniques.

Pulse oximetry and pulse waveform data were collected from pregnant patients and healthy nonpregnant volunteers. A disposable Nellcor pulse oximeter sensor (D-25) was placed on the first or second toe, a location chosen to minimize motion artifact and interference. In addition, when the duration of labor permitted, recordings were taken from a finger or the bridge of the nose. Data were continuously recorded using a Nellcor N-100 pulse oximeter (Haywood, Calif.) attached to a Nellcor chart recorder (N-9000). Processed analog waveform data from the N-100 pulse oximeter were also routed to a Gould two-channel strip chart recorder.

An additional group of parturients and volunteers was studied using the N-100 and the N-200 devices simultaneously: a D-25 probe was placed on the left and right corresponding toe and connected to these devices. After a series of Valsalva maneuvers, each machine was switched to the contralateral toe and data were collected during a similar number of Valsalva maneuvers. Differences in oximeter performance with respect to the onset and resolution of the PTO mode were noted, as were differences in the data reported by the respective devices.

All pregnant patients were actively pushing during the late second stage of labor and had adequate epidural analgesia. Patients were placed in a semisitting position in a birthing bed and were free to flex at the hips and knees. Other than attaching the sensors and obtaining consent, the investigators did not interfere with the interactions between the obstetric staff and parturient or with the progress and management of labor. The study protocol required notification to the medical staff in the event of oximeter saturations below 85%. Expulsive efforts were coached in a fashion typical of our practice at the University of Virginia. At the onset of each contraction, the patient was instructed to take a deep breath and bear down for a slow count of 10, then rapidly exhale and perform another Valsalva maneuver; the sequence was usually repeated for a third time. Afterwards, the patient was instructed to relax and breathe normally. In this report, several Valsalva maneuvers performed in rapid succession are referred to as a "salvo."

Nonpregnant volunteers were selected and studied in such a manner as to eliminate factors specific to the pregnant patient in labor. Thus, male volunteers were included, the Valsalva maneuver was performed supine without flexion of the hips and knees, volunteers did not receive epidural analgesia, and subjects were coached to rest between each Valsalva maneuver rather than perform a complete three Valsalva salvo.

The peripheral circulatory effects of the Valsalva maneuver were studied in healthy volunteers. Occlusive venous impedance plethysmography studies of the lower extremity were conducted with an IPG-100 plethysmograph (Codman and Shurtlett, Inc., Randolph, Mass.) to assess venous capacitance and confirm venous patency. Electrical impedance was measured by means of circumferential electrodes placed

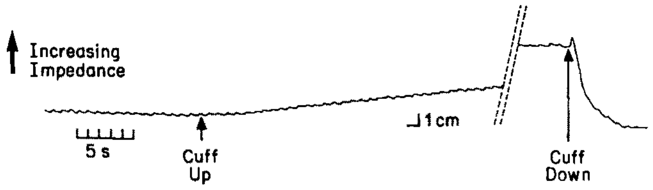

Figure 1. Normal venous impedance plethysmograph. With the cuff inflated, venous drainage from the leg is blocked and the increased venous volume causes an increase in impedance. When the cuff is released, there is a rapid decrease in impedance as blood empties from the engorged leg veins. The total time for this measurement was 2 min.

around the lower leg. To assess lower extremity venous drainage, a proximal thigh cuff was inflated to 60 mmHg so that venous outflow from the leg was obstructed. As blood volume in the leg increased, changes in lower leg electrical capacitance were recorded (Figure 1). Upon cuff deflation, the release of pooled blood in the leg was associated with a sharp decrease in capacitance. A normal occlusive venous impedance plethysmographic study was confirmed for each subject, then impedance measurements were recorded during several salvos.

A pulse volume recorder (Life Sciences, Inc., Greenwich, Conn.) was used to assess arterial pulse volume amplitude in the lower extremities. This device consists of an inelastic circumferential cuff placed around the toe or calf, filled with a known volume of air, and connected to a calibrated pressure transducer linked to a strip chart recorder. With every arterial pulsation a volume of blood enters the extremity thereby displacing a volume of air from the surrounding cuff. The resulting waveform recordings are characteristic for the arterial circulation (Figure 2, upper trace). Pulse amplitude was determined by drawing a line through the plateau portion (diastole) of the recorded waveform and measuring the height of the systolic trace from the preceding diastolic level. Noise within the pulsatile signal was determined by measuring the distance between the apex and nadir of the trace during the diastolic phase of the trace.

The nonpregnant volunteers studied in this manner did not receive epidural analgesia nor did they flex the hips or knees during the Valsalva maneuver. Every volunteer performed each salvo in similar fashion to the pregnant subjects; three 10-s Valsalva maneuvers were performed separated by single deep breaths. Venous impedance plethysmographic data were collected independently from pulse volume recorder data.

All data are reported as mean ± standard deviation where appropriate. Statistical significance is defined as $P < 0.05$ and was determined using one-way analysis of variance.

Results

Demographic data are presented in Table 1. The pregnant subjects were younger ($P < 0.02$) than the nonpregnant controls or the noninvasive laboratory volunteers. Four male volunteers were included in each of the latter groups. An additional four pregnant and six nonpregnant individuals were studied using the N-100 and N-200 oximeters simultaneously. As the performance of each device was compared in the same patient, and not between patients, no comparative demographic data are presented for these subjects.

The pulse oximeter shifted into the PTO mode in close association with the Valsalva maneuver in all nine pregnant patients, occurring in 41 of 42 salvos. In 27 salvos (64%), the first Valsalva maneuver caused the onset of the PTO mode (Table 2). In the 15 salvos in which the oximeter was not interrupted during the first Valsalva maneuver, 12 reverted to the PTO mode during the second Valsalva maneuver. On two occasions the PTO mode did not occur until the third Valsalva maneuver of the salvo. Thus, in a total of 130 separate Valsalva maneuvers performed by this group, the PTO mode occurred during 108 maneuvers (83%). In nonpregnant volunteers, the Valsalva maneuver resulted in the pulse oximeter shifting into PTO mode in 8 of 9 subjects. Of a total of 40 Valsalva maneuvers, entry into the PTO mode occurred in 26 (65%: NS vs first Valsalva maneuver in pregnant subjects).

The processed N-100 analog plethysmographic waveform exhibited characteristic patterns in association with the Valsalva maneuver and were qualitatively indistinguishable in pregnant as opposed to nonpregnant subjects (Figure 3). During every salvo recorded, there was a progressive decrease in waveform amplitude and loss of waveform definition, and the appearance of the PTO mode was temporally related to these changes. In addition, the beginning of each Valsalva maneuver was associated with a decrease in the baseline of the waveform that appeared to coincide with the inspiratory gasp preceding each Valsalva maneuver.

In the 10 patients studied using both the N-100 and N-200 pulse oximeters simultaneously, no differences were noted with respect to time of onset or duration of the PTO mode. In addition, there were no differences in the pulse rate or oxygen saturation data reported by either instrument at any time during the study.

Pulse volume data (Table 3) were analyzed by evaluating the relative change in pulse amplitudes compared with baseline amplitudes during the progression of the Valsalva maneuver. Although absolute volume amplitudes were lower in the toe than in

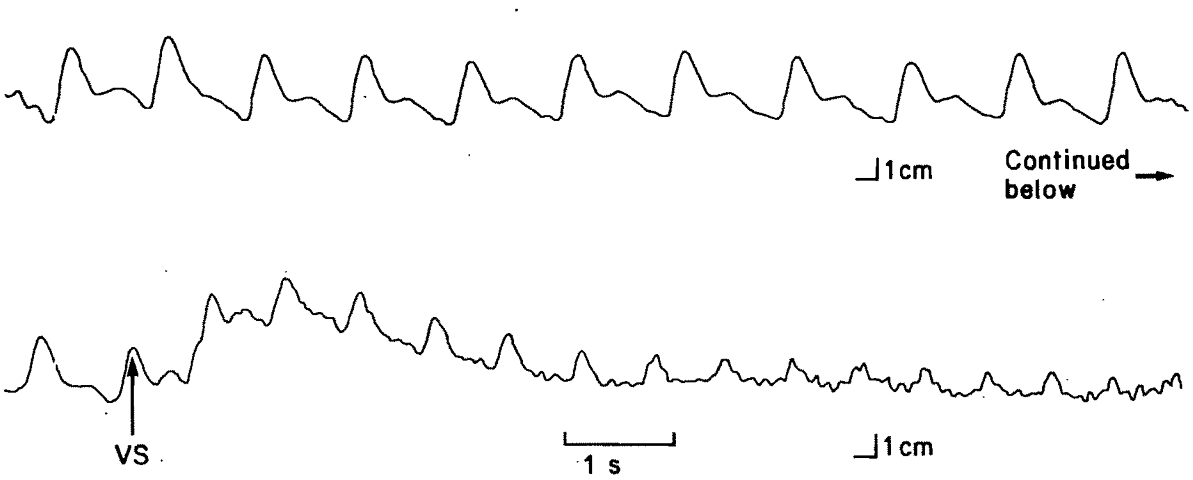

Figure 2. Pulse volume recording during a single Valsalva maneuver. The *upper trace* is during quiet breathing, and the *lower trace* is from the same subject during a Valsalva maneuver that begins at VS (Valsalva start).

Table 1. Characteristics of Subjects

	Pregnant subjects	Nonpregnant controls	Noninvasive laboratory volunteers
n	8	9	9
Age (yr)	24 ± 3.5[a]	29 ± 4.1	31 ± 4.2
Weight (kg)	70 ± 13.7	71 ± 13.4	70 ± 13.7
Sex (male/female)	0/8[b]	4/5	4/5

[a] $P < 0.02$ vs both nonpregnant controls and noninvasive laboratory volunteers.
[b] $P < 0.05$ vs both nonpregnant controls and noninvasive laboratory volunteers.

Table 2. Frequency of Occurrence of Pulse Time-Out Mode During Valsalva Maneuvers

	PTO mode	Valsalva maneuvers	Percent
Pregnant subjects	108	130	83
Pregnant, first Valsalva of each salvo	27	42	64
Nonpregnant controls	26	40	65

PTO, pulse time-out.

Table 3. Analysis of Pulse Volume Recordings

Time to 50% decrease in peak-to-trough amplitude	5.7 ± 2.7 s
Ratio of minimum pulse amplitude to resting amplitude	0.33 ± 0.12
Signal-to-noise ratio of pulse amplitude during Valsalva	2.5:1

the lower leg, the relative changes were similar at each location; consequently all pulse volume recorder data have been pooled.

The inspiratory gasp preceding each Valsalva maneuver was associated with a detectable decrease in pulse volume amplitude for one or two heartbeats (Figure 2, point VS). As soon as the glottis was closed and forced exhalation initiated, there was an immediate increase in pulse volume amplitude and an upward shift in diastolic volume baseline (Figure 2, lower trace). These changes were transient (2–3 s) and were followed by a return to the original diastolic baseline and a marked decrease in pulse volumes. Progressive diminution in the peak-to-trough amplitude occurred, so that within 5.7 (±2.7) s the peak-to-trough amplitude was less than 50% of the resting pulse amplitude. The ratio of the minimum pulse volume amplitude during the Valsalva maneuver to the resting pulse volume amplitude was 0.33 (±0.12). During the Valsalva maneuver, noise within the pulsatile signal represented 40% (±13%) of the total signal amplitude for a 2.5:1 signal-to-noise ratio. With release of the Valsalva, there was restoration of normal pulse volume amplitude and shape within several heartbeats.

Even though the peak-to-trough volume amplitude decreased during all Valsalva maneuvers, there was a discernable pulse volume waveform in all subjects but one. In this individual, there was complete ablation of the pulse volume waveform and the subject temporarily lost consciousness.

Venous impedance plethysmographs revealed a variable and unpredictable perturbation in venous blood volume with the initiation and termination of each Valsalva maneuver. This change lasted 1–2 s and was followed by an immediate return to baseline (Figure 4). There was no measurable increase in impedance above resting levels in any subject during any Valsalva maneuver, implying that little change occurred in total lower extremity blood volume. Furthermore, the lack of change in impedance on release of the Valsalva suggests little or no venous pooling during the maneuver.

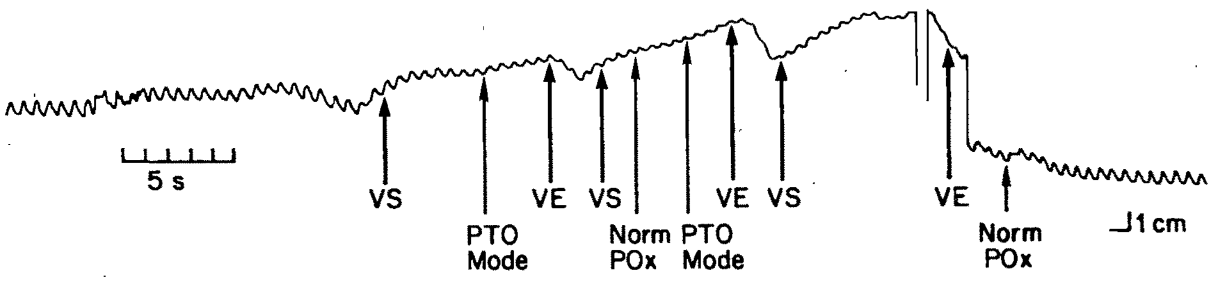

Figure 3. Nellcor plethysmograph from a pregnant patient. There is a transient decrease in the waveform baseline just before the start of the Valsalva maneuver (VS). There is a progressive loss of waveform amplitude during each Valsalva maneuver, reading from left to right. The onset of the PTO mode is indicated, and the return of the bouncing dot display is designated Norm POx. VE marks the end of each Valsalva maneuver. The interruption in the trace and the abrupt shift in baseline at the end of the third Valsalva maneuver reflect software adjustments by the oximeter.

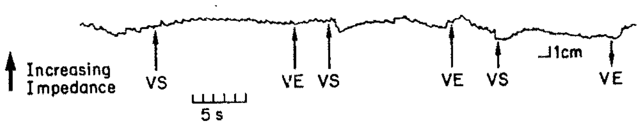

Figure 4. Venous impedance plethysmograph during a three-Valsalva salvo. The beginning and end of each individual Valsalva maneuver are indicated by VS and VE, respectively. The lack of a decrease in impedance with release of the Valsalva, as compared with Figure 1, suggests the absence of venous pooling.

Discussion

The impetus for this study was a report in the obstetric literature of pulse oximetry use during the second stage of labor that made no mention of oximeter performance during periods of Valsalva maneuvers (2). The present study demonstrates that data interruption is a consistent phenomenon related to the hemodynamic consequences of the Valsalva maneuver and is independent of the pregnant state.

The physiology of the Valsalva maneuver is associated with abrupt hemodynamic changes as demonstrated by the pulse volume recordings. These changes interface with predetermined criteria for pulse wave identification and uniformity during pulse oximetry, thereby causing an interruption of transmission of oxygen saturation data. This represents yet another clinical situation in which the limitations of the oximeter are exceeded, and occurs in the realm of oximeter "artifact management," the most difficult engineering problem in noninvasive oximetry (3). The significant decrease in pulse volume amplitude during the Valsalva maneuver results in a signal that, to the oximeter, is indistinguishable from background noise.

Monitoring problems can occur when using pulse oximetry in patients who are hypovolemic, hypotensive, or hypothermic. In all these cases, the technical problem is a low signal-to-noise ratio as the diminished peripheral pulse ("the ripple") is lost in a "sea" of background absorbance from other tissues and electromagnetic artifact (3). Although healthy parturients are hypervolemic, vasodilated, and peripherally warm, greatly diminished peripheral pulse strength during the Valsalva maneuver results in a signal that is too small for reliable operation of the pulse oximeter.

The abrupt changes seen in the pulse volume recordings have a physiologic basis. At the start of each Valsalva maneuver, a rapid inspiratory gasp decreases intrathoracic pressure. With extrathoracic pressure unchanged, the net result is an increase in afterload. Both cardiac output and peripheral arterial blood pressure decrease with inspiration (5–7), and this phenomenon is recorded as a brief decrease in pulse volume amplitude (Figure 2). With initiation of the Valsalva maneuver, there is a sudden increase in intrathoracic pressure; extrathoracic pressures remain unchanged. This results in an effective decrease in afterload and an increase in stroke volume and cardiac output. The tone of the precapillary resistance vessels prevents this increase in cardiac output from being rapidly transferred to the venous circulation, and there is a transient rise in diastolic volume within the arterial circulation (Figure 2, lower trace). Within few seconds, the diastolic pulse volume returns to baseline as blood empties into the venous circulation, and there is a superimposed flattening of the pulse volume recorder waveform that persists until the end of the Valsalva maneuver. This reflects a period of decreased stroke volume resulting from inadequate preload as blood return to the right side of the heart is impeded by the increased intrathoracic pressure (8). In cases of very strenuous effort, as seen in one subject with complete ablation of the peripheral pulse, cardiac output can be so impaired as to affect cerebral perfusion.

As measured by the pulse oximeter, these changes in plethysmograph morphology are clearly significant, triggering the cycling of the hardware and software (the PTO mode) to optimize signal acquisition. While the pulse oximeter is attempting to reacquire usable plethysmograph data during the plateau phase of the Valsalva maneuver, the Valsalva is suddenly released causing yet another series of rapid changes, the most notable of which is a precipitous increase in the pulse amplitude that occurs over a period of two to three heartbeats. Through all this, the pulse oximeter continues to collect and process pulse waveforms until five consecutive beats meet the criteria necessary for information to be passed on to the front panel.

Severinghaus and Spellman (9) have shown that pulse oximeter failure during hypotension is related more to decreased pulse pressure than to the absolute level of systolic arterial blood pressure, and a decrease in pulse pressure can be caused by a decrease in systolic pressure as well as an increase in diastolic pressure. Our initial hypothesis surmised that the PTO mode during the Valsalva maneuver was induced by a decrease in pulse pressure due to a large increase in venous pressure in the extremities. However, the lack of demonstrable venous congestion during the brief Valsalva maneuvers, as determined by venous impedance plethysmography, fails to support this hypothesis. Previous studies had reported a 20 mm Hg increase in venous pressure during the Valsalva maneuver; however, venous volumes were not measured and pressures were measured at the end of a single 30-s Valsalva maneuver, as compared with serial 10-s efforts in the present study (10). In two other studies in which a circumferential blood pressure cuff was utilized to assess pulse oximeter function, the PTO mode did not occur until arterial pulsations were almost completely obliterated, despite the presence of venous congestion (9,11). Venous congestion can influence oximeter function; inflation of a brachial cuff to diastolic pressures for several minutes resulted in Nellcor N-200 oximeter failure at a systolic pressure of 60 mm Hg compared with 40 mm Hg when rapid cuff inflation without a period of venous outflow obstruction was tested (9). During brief Valsalva maneuvers, however, it appears that venous congestion is of minimal consequence.

The brief and variable perturbations in venous volume in the extremities at the onset of the Valsalva maneuver (Figure 4) probably reflect the influence of several factors, including peripheral autonomic circulatory reflexes triggered by an inspiratory gasp (12) and augmented venous outflow associated with a transitory fall in intrathoracic pressure as inhalation begins. The steady venous volume during the plateau phase of the Valsalva maneuver probably represents a balance between impaired venous outflow from the extremities during the period of increased intrathoracic pressure coupled with reduced arterial inflow.

The Nellcor N-200 oximeter was used alongside the N-100 to evaluate a technical hypothesis for our observations. That is, the N-100 was unable to adequately capture and analyze an otherwise usable pulse waveform (despite circulatory changes) because of inadequate IR data. Although the N-200 oximeter allows independent control of IR data acquisition, the N-100 and N-200 performed in an identical fashion. Therefore, independent IR light control, and presumably enhanced pulse morphology acquisition, could not overcome the circulatory flux seen during the Valsalva maneuver. Although we have not studied pulse oximeters built by other manufacturers, our findings allow us to predict that, given the current state of pulse oximeter technology, all instruments will be similarly hampered when collecting data during the Valsalva maneuver.

In terms of implications for obstetric practice, this study indicates that standard protocols for "pushing" during the second stage of labor are associated with marked but transient reductions in maternal stroke volume. As these expulsive efforts are performed during periods of uterine contraction when uterine blood flow is already greatly decreased, the additional factor of decreased maternal cardiac output is probably of no significance to the well-being of the fetus. The pulse oximeter may be of some utility as a biofeedback device, in that strenuous expulsive efforts can be expected to trigger the PTO mode and the loss of the audible signal can be readily monitored by the patient and staff.

This study demonstrates that the Valsalva maneuver is associated with marked decreases in pulse volume amplitude, resulting in an impaired signal-to-noise ratio, as well as abrupt changes in peripheral arterial blood volumes, thus producing a nonuniform pulse plethysmograph. These physiologic changes in arterial hemodynamics result in failure of pulse signal identification by the pulse oximeter.

The authors thank their colleagues in the Department of Obstetrics and Gynecology and Connie Sanders and Joan Branscome of the Peripheral Vascular Laboratory for making this study possible.

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Anesthetic Modification of Hemodynamic and Neuroendocrine Stress Responses to Cesarean Delivery in Women With Severe Preeclampsia

Jaya Ramanathan, MD, Phyllis Coleman, RN, and Baha Sibai, MD

Departments of Anesthesiology and Obstetrics and Gynecology, University of Tennessee, Memphis, Memphis, Tennessee

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We conducted a prospective evaluation of the comparative effects of lumbar epidural and general anesthesia on the hemodynamic and neuroendocrine stress response to cesarean delivery in 21 women with severe preeclampsia. In the epidural group (n = 11), anesthesia extending to the T-4 dermatome level was obtained using 2% plain lidocaine in divided doses. In the general anesthesia group (n = 10), anesthesia was induced after pretreatment with labetalol or nitroglycerine. In the epidural group, mean arterial pressure (MAP) gradually decreased from 133.3 ± 5.6 mm Hg to 119 ± 4.4 mm Hg ($P < 0.002$). After pretreatment with labetalol or nitroglycerine, MAP in the general group decreased from 131.5 ± 4.9 mm Hg to 112.2 ± 3.5 mm Hg ($P < 0.001$). At skin incision (after tracheal intubation), MAP increased from 112.2 ± 3.5 mm Hg to 143 ± 5.4 mm Hg ($P < 0.001$); however, this was not significantly different from baseline MAP. In the epidural group, there were no further changes in MAP. The difference in MAP at skin incision and postpartum period between the two groups was significant ($P < 0.004$ and $P < 0.009$, respectively). In the general anesthesia group, both adrenocorticotropic hormone and β-endorphin-like immunoactivity increased significantly from base levels at skin incision. The catecholamines also increased significantly and remained so throughout the study period. In the epidural group, the concentrations of these hormones decreased or remained unchanged. Cortisol concentrations in the postpartum period were significantly higher in both groups. There were more neonates with Apgar scores of less than 7 at 1 min in the general anesthesia group. Stress hormone concentrations in the neonates in both groups were similar, and no correlations were found between maternal and neonatal hormone concentrations in the two groups. We conclude that epidural anesthesia extending to the T-4 dermatome caused blunting of the hemodynamic and neuroendocrine stress responses to cesarean delivery in women with severe preeclampsia. The anesthetic technique did not alter the neonatal stress hormone concentrations at birth.

(Anesth Analg 1991;73:772–9)

Several investigators (1–3) have shown that in healthy normotensive parturients undergoing cesarean delivery, tracheal intubation and surgical stimulation during general anesthesia elicit severe hemodynamic and neuroendocrine stress responses, such as increases in maternal mean arterial pressure (MAP), heart rate, and plasma concentrations of stress-related hormones such as adrenocorticotropic hormone (ACTH), cortisol, glucagon, and catecholamines. On the other hand, epidural anesthesia extending to the sixth thoracic dermatome effectively blunts the stress responses to anesthesia and surgery (1–3). More than a decade ago, Hodgkinson et al. (4) demonstrated that in women with severe preeclampsia undergoing cesarean delivery, significant increases in MAP, pulmonary capillary wedge pressure, and pulmonary artery pressure occurred only in those receiving general anesthesia, whereas in women receiving epidural anesthesia these variables remained unchanged. Studies have also shown that in women with severe preeclampsia administration of epidural anesthesia for analgesia during labor decreases catecholamine levels (5) and improves intervillous blood flow (6). Despite these favorable results, many physicians (7,8) continue to believe that administration of epidural anesthesia in women with severe preeclampsia is detrimental to both mother and fetus owing to possible profound hypotension. No prospective studies have been conducted compar-

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Presented in part at the annual meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, 1990.

Accepted for publication August 5, 1991.

Address correspondence to Dr. Ramanathan, Department of Anesthesiology, The University of Tennessee, Memphis, 877 Jefferson Avenue, Ground Floor, Chandler Building, Memphis, TN 38163.

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0003-2999/91/$3.50

ing both hemodynamic and hormonal changes in women with severe preeclampsia receiving either epidural or general anesthesia for cesarean delivery. The purpose of this investigation was to compare the anesthetic modification of maternal hemodynamic and neuroendocrine responses to cesarean delivery and neonatal outcome in women with severe preeclampsia receiving epidural versus general anesthesia.

Methods

Our study was conducted in 21 women with severe preeclampsia who were scheduled to undergo cesarean section under either epidural or general anesthesia. All patients had severe preeclampsia with persistent increases of arterial blood pressures (systolic ≥ 160 mm Hg, diastolic ≥ 110 mm Hg) and proteinuria of more than 5 g in 24 h (3+ or 4+). The original protocol with random assignment of patients to either epidural or general anesthesia groups was denied approval by the Institutional Review Board. Therefore, the protocol and consent forms were revised and, as per the Institutional Review Board requirement, patients participated in making the decision as to which anesthetic they would receive and were assigned either epidural (EA) or general anesthesia (GA) according to their preference. Women in active labor, those with coagulation abnormalities, placental abruption, chronic hypertension, and other medical complications were excluded from the study.

All patients were admitted by the obstetric service for evaluation and treatment. Laboratory investigations included complete blood count, coagulation profile including platelet function tests, renal and liver function tests, and urinalysis. Maternal electrocardiogram was monitored throughout as was fetal heart rate, until the beginning of surgery. Arterial blood pressure was measured by means of indwelling radial artery catheters in all women. In addition, central venous pressure lines were inserted in 19 patients. In the two remaining patients who had oliguria unresponsive to the intravenous administration of crystalloids, left-sided cardiac filling pressures were monitored by means of pulmonary artery catheter. For prophylaxis against seizures, all patients received magnesium sulfate therapy according to a standard protocol consisting of an initial intravenous dose of 6 g followed by an infusion of 2–3 g/h. In addition, intravenous hydralazine in 5-mg boluses up to a total dose of 15–20 mg were administered by obstetricians to 11 patients to decrease the diastolic blood pressure to below 100 mm Hg. Four patients received nitroglycerine infusions at a rate of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Preoperative medication consisted of antacid therapy with ranitidine, 50 mg IM, and sodium citrate, 30 mL orally, 1 h before the procedure. In the EA group, all women received dextrose-free crystalloid solutions intravenously, and central venous pressures were maintained at 4–6 cm H_2O. An epidural catheter was inserted into the second or third lumbar interspace and advanced 3–4 cm cephalad. After a test dose of 4 mL of 2% plain lidocaine, an additional 18–20 mL was injected in divided doses to obtain a T-4 sensory block. All patients were placed in 15° left lateral tilt and oxygen was administered via a face mask. Maternal hemoglobin oxygen saturation was continuously monitored using finger pulse oximetry. A decrease of maternal systolic pressure below 100 mm Hg or a decrease in MAP by 20% below baseline values was treated with intravenous ephedrine in 5-mg boluses and further intravenous crystalloid administration. After the delivery, midazolam in doses of 1–2 mg was administered to the mothers for sedation. In the GA group, patients were placed on the operating table in 15° left lateral tilt and breathed oxygen for a minimum of 4–5 min. To avoid the severe hypertensive response to tracheal intubation, they were pretreated in the following manner: six patients received an initial intravenous dose of 20 mg of labetalol, followed by 10-mg boluses up to a total dose of 1 mg/kg. The remaining four patients treated earlier with nitroglycerine, were given the drug at a rate of 0.5–1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before induction of anesthesia. Both drugs were given to decrease the diastolic pressures below 100 mm Hg or MAP by 20% from baseline values. This was followed by a rapid-sequence induction of anesthesia with thiopental, 4 mg/kg IV, and tracheal intubation was facilitated by succinylcholine, 1 mg/kg IV. Cricoid pressure was applied until the correct placement of the endotracheal tube was verified by auscultation of the lungs and end-tidal CO_2 monitoring. Anesthesia was maintained with 50% nitrous oxide in oxygen and 0.5% isoflurane until delivery. Afterwards, anesthesia was augmented by increasing the N_2O concentration to 67% in O_2 and administering fentanyl intravenously in doses of 50–100 μg as required. Induction-to-delivery interval, uterine incision-to-delivery interval, duration of surgery, and total volume of fluids administered intravenously were noted. At delivery, Apgar scores were assigned by neonatologists who were unaware of the study protocol. In addition, neonatal gestational age, birth weight, umbilical artery pH, Po_2, Pco_2, and base deficit were also recorded. Women in both groups were observed for a minimum of 24–48 h in the recovery room or intensive care unit where hemodynamic variables and urine output were closely monitored.

Arterial blood samples were drawn from the first six patients in the GA group and from seven patients in the EA group for estimation of ACTH concentrations, β-endorphin-like immunoactivity, and catecholamines and cortisol concentrations at the following intervals: (a) before induction (baseline), (b) at skin incision, (c) at delivery (maternal and umbilical), and (d) 120 min after induction of anesthesia (postpartum). Blood samples for analysis of ACTH and β-endorphin-like immunoactivity were collected in prechilled tubes containing ethylene diaminetetraacetate. For measurement of catecholamine and cortisol concentrations, samples were collected in heparinized tubes. All blood samples were centrifuged at 4°C for 20 min. The plasma was transferred to plastic vials and stored at −20°C until analysis. Adrenocorticotropic hormone was measured by an equilibrium radioimmunoassay using a rabbit ACTH antibody that was allowed to incubate with sample and tracer for 16–24 h. Antibody-bound ACTH was separated by a polyethelene glycol–preprecipitated second antibody. The level of ACTH in the sample was determined by comparing the radioactive count to a standard curve. For measurement of β-endorphin-like immunoactivity, extraction from plasma samples was performed with silica. The peptides were then eluted with acidified acetone and the levels were determined by radioimmunoassay. Cortisol concentrations were determined by using cortisol kits marketed under the name Gamma Coat 125 1-cortisol radioimmunoassay kits (Clinical Assays, Cambridge, Mass.). For catecholamine concentrations, the samples were spiked with an internal standard and adsorbed on alumina at alkaline pH. The catecholamines were desorbed with perchloric acid and chromatographed on a C8 column by high-pressure liquid chromatography. Statistical analysis of the data was done using the *t*-test, analysis of variance for repeated measures, and Pearson correlation, $P < 0.05$ being considered significant. All values are expressed as mean ± SEM.

Table 1. Maternal Demographic and Intraoperative Data

	Epidural anesthesia ($n = 11$)	General anesthesia ($n = 10$)
Age (yr)	19.3 ± 2.3	18.8 ± 2
Height (cm)	160 ± 1.5	165 ± 2.0
Weight (kg)	65.8 ± 2.5	67.3 ± 1.9
Parity		
Primiparas	11	10
Multiparas	0	0
ID interval (min)	14 ± 0.7	4.4 ± 0.6[a]
UD interval (min)	1.7 ± 0.2	1.4 ± 0.3
Total volume of fluids (mL)	1932 ± 58	1300 ± 63[b]
Duration of surgery (min)	78 ± 4	82 ± 5

ID, induction of anesthesia to delivery; UD, uterine incision to delivery. Values are mean ± SEM.
[a] $P < 0.01$.
[b] $P < 0.001$.

Table 2. Pertinent Clinical and Laboratory Findings[a]

Findings	Epidural anesthesia ($n = 11$)	General anesthesia ($n = 10$)
Mean arterial pressure (mm Hg)	133 ± 5.7	131 ± 3.1
Proteinuria ≥ 5 g/24 h	Present	Present
Pregnancies with IUGR	4/11	3/10
Pregnancies with oligohydramnios	4/11	2/10
Platelets ($\times 10^3/\text{mm}^3$)	195 ± 6.0	205 ± 3.4
Bleeding time (min)	8 ± 0.5	7.3 ± 0.4
BUN (mg/dL)	12.8 ± 1.5	14.0 ± 1.6
Creatinine (mg/dL)	1.1 ± 0.1	0.9 ± 0.1
Uric acid (mg/dL)	8.0 ± 0.7	7.2 ± 0.6
Total bilirubin (mg/dL)	0.6 ± 0.1	0.5 ± 0.1
LDH (IU/L)	195 ± 48	161 ± 40
SGOT (IU/L)	45 ± 6.3	43 ± 5.7

IUGR, intrauterine growth retardation, BUN, blood urea nitrogen; LDH, lactic dehydrogenase; SGOT, serum glutamic oxaloacetic transaminase.
[a] Values are mean ± SEM. There were no significant differences.

Results

Of the 21 women studied, 10 received general anesthesia and 11 received epidural anesthesia. Demographic and intraoperative data are shown in Table 1. There were no significant differences in age, height, weight, and parity between the two groups. The induction-to-delivery intervals were significantly more prolonged in the EA group ($P < 0.01$), and uterine incision-to-delivery intervals and duration of surgery were similar in the two groups. Total volume of fluids administered was significantly higher in the EA group ($P < 0.001$) (Table 1). Pertinent clinical and laboratory findings are given in Table 2. No significant differences were present in MAP, degree of proteinuria, platelet, renal, and liver function tests, and the number of pregnancies with intrauterine growth retardation and oligohydramnios in the two groups (Table 2). Maternal arterial pressure was continuously monitored by means of an indwelling radial artery catheter. The values for MAP at the time of blood sampling for hormone concentrations, i.e., at baseline, before induction, at skin incision, at delivery, and in the postpartum period for both groups, are depicted in Figure 1. Baseline MAPs were similar in the two groups. In the EA group, MAP decreased from 133.3 ± 5.6 mm Hg to 115.4 ± 6 mm Hg when the epidural block reached the T-4 dermatome ($P < 0.01$), and further to 108.8 ± 3.6 mm Hg at the time of delivery ($P < 0.01$). This constituted 18%–20% reduction from baseline MAPs. One patient had a sudden decrease in systolic blood pressure from 162 to 104 mm Hg. Immediate intravenous administration of two 5-mg boluses of ephedrine and rapid crystalloid administration prevented further decreases in

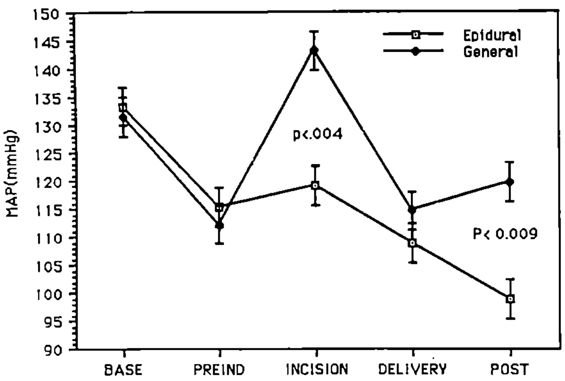

Figure 1. Changes in mean arterial pressure (MAP) in the study groups. BASE = baseline values; PREIND: in the GA group = MAP obtained after pretreatment with labetalol or nitroglycerine and in the EA group = MAP with T-4 sensory block; INCISION = at skin incision; DELIVERY = at delivery of infant; POST = postpartum.

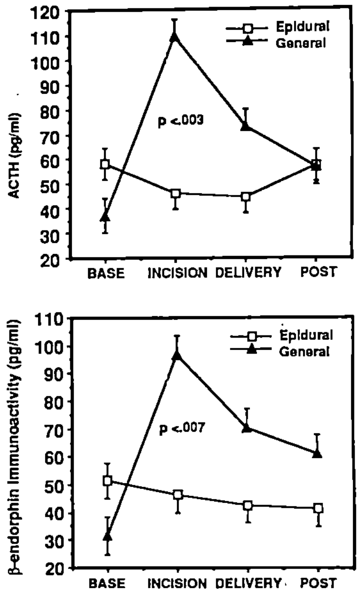

Figure 2. Changes in levels of ACTH and β-endorphin-like immunoactivity in the two study groups: before induction of anesthesia (BASE), at skin incision (INCISION), at delivery of infant (DELIVERY), and postpartum (POST).

MAP. None of the remaining 10 patients in this group required ephedrine. In the GA group, no significant differences were present in the data obtained from the six patients who received labetalol and the four treated with nitroglycerine infusions, hence the data were combined. Despite earlier treatment with hydralazine and nitroglycerine, diastolic pressures were elevated (>100 mm Hg) in the majority of patients on arrival in the operating room. Pretreatment with labetalol or nitroglycerine decreased MAP from 131.5 ± 3.5 mm Hg to 112.2 ± 3.5 mm Hg ($P < 0.001$) (Figure 1). After induction of anesthesia, tracheal intubation was easily performed in all cases within 30 s of onset of succinylcholine-induced muscle paralysis. Transient but significant increases in MAP occurred at skin incision (immediately after tracheal intubation) to 143 ± 5.4 mm Hg ($P < 0.001$). However, MAP at skin incision was not significantly different from baseline MAP. Significant differences were present in MAP between the EA and GA groups at skin incision ($P < 0.004$) and in the postpartum period ($P < 0.009$).

The levels of ACTH and β-endorphin-like immunoactivity are shown in Figure 2. Baseline values for both hormones were similar in the two groups. At skin incision, in the GA group, there were significant elevations of both ACTH and β-endorphin levels from baseline values of 37.0 ± 5.4 pg/mL and 31.5 ± 5.7 pg/mL to 109.1 ± 18.17 pg/mL and 96.6 ± 34.7 pg/mL, respectively ($P < 0.0001$). In contrast, in the EA group there were no significant changes in the concentrations of either of these hormones during the study period. The differences between the EA and GA groups at skin incision were significant ($P < 0.003$ and $P < 0.007$, respectively).

Catecholamine concentrations changed in the following manner: there were no differences in baseline concentrations of epinephrine, norepinephrine, and dopamine between the two groups (Figure 3). In the GA group, there was significant increase of epinephrine concentrations at skin incision from 71.0 ± 20.7 pg/mL to 252.3 ± 70.5 pg/mL ($P < 0.001$) and norepinephrine values increased from 567.6 ± 176.0 pg/mL to 886.3 ± 223.32 pg/mL ($P < 0.001$). Dopamine levels increased steadily from a baseline value of 30.3 ± 9.7 pg/mL to 110.3 ± 22.1 pg/mL in the postpartum period ($P < 0.0001$). In the EA group, no significant changes were observed in concentrations of epinephrine and dopamine during the study period. Norepinephrine concentrations decreased from 493.28 ± 81.24 pg/mL to 296.28 ± 80.51 pg/mL at skin incision and continued to decline thereafter. During surgery, differences in epinephrine, norepinephrine, and dopamine concentrations between the groups were significant. Cortisol concentrations increased in both groups, the increases becoming significant from baseline levels only in the postpartum period ($P < 0.001$ and $P < 0.006$, respectively) (Figure 4).

Neonatal gestational age and birth weight were similar in the two groups (Table 3). The number of babies with Apgar scores less than 7 was significantly higher in the GA group at 1 min but not at 5 min. Umbilical artery pH, Po_2, and Pco_2 were similar in both groups. In contrast, base deficit was significantly higher in neonates in the GA group ($P < 0.02$) (Table 3). Plasma concentrations of ACTH, catechol-

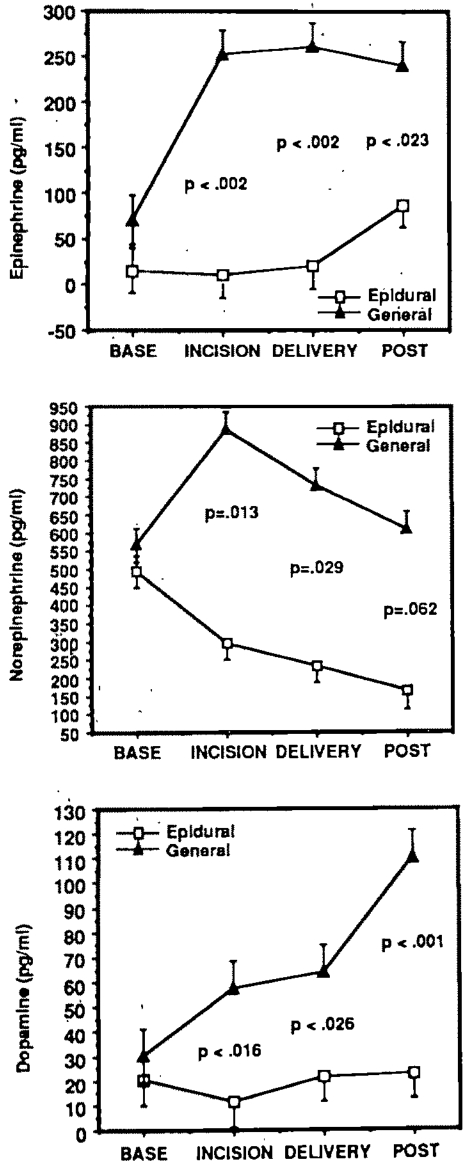

Figure 3. Changes in the catecholamine levels in the study groups: before induction of anesthesia (BASE), at skin incision (INCISION), at delivery of infant (DELIVERY), and postpartum (POST).

amines, and cortisol were similar in the two groups of infants and there were no significant correlations between maternal and neonatal stress hormone levels. β-Endorphin immunoactivity tended to be higher in the infants in the GA group compared with the EA group (83.5 ± 17.7 pg/mL vs 43.57 ± 13.41 pg/mL), but this did not achieve statistical significance ($P = 0.057$). A moderate correlation was present between neonatal ACTH and β-endorphin ($r = 0.62$, $P < 0.01$) and highly significant negative correlations were present between neonatal β-endorphin and Po_2 ($r = 0.7$, $P < 0.0003$) and pH ($r = 0.89$, $P < 0.0001$) at birth.

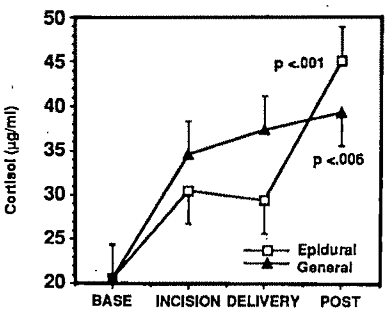

Figure 4. Changes in levels of cortisol in the two study groups: before induction of anesthesia (BASE), at skin incision (INCISION), at delivery of infant (DELIVERY), and postpartum (POST).

Table 3. Neonatal Characteristics

Characteristics	Epidural anesthesia ($n = 11$)	General anesthesia ($n = 10$)
Gestational age (wk)	32.7 ± 0.6	33.2 ± 0.4
Birth weight (g)	2216 ± 160	2229 ± 210
Apgar score <7 at 1 min	0	6[a]
Apgar score <7 at 5 min	0	2
UA		
pH	7.29 ± 0.08	7.22 ± 0.01
Po_2 (mm Hg)	26 ± 2.0	27 ± 1.5
Pco_2 (mm Hg)	51 ± 1.4	48 ± 2.2
BD (mEq/L)	2.44 ± 0.3	4.3 ± 0.69[b]

UA, umbilical artery; Po_2, oxygen tension; Pco_2, carbon dioxide tension; BD, base deficit.
Values are mean ± SEM.
[a] $P < 0.05$.
[b] $P < 0.02$.

Discussion

The results of our study indicate that lumbar epidural anesthesia extending to the fourth thoracic dermatome level causes blunting of the hemodynamic and neuroendocrine stress responses during cesarean delivery in nonlaboring women with severe preeclampsia. In contrast, tracheal intubation followed by surgical stimulation under light general anesthesia elicits these responses in an exaggerated manner, with significant increases in the stress hormone concentrations and maternal MAP. Although this study was not strictly randomized, our study groups were similar with respect to the severity of preeclampsia. In addition to the standard clinical criteria, such as severe hypertension and proteinuria, other clinical and laboratory indicators of the severity of the disease process, such as the platelet function, liver and renal functions, and the incidence of intrauterine growth retardation and oligohydramnios, were similar in the two groups.

Hemodynamic Changes During Anesthesia

In the GA group, after pretreatment with antihypertensive agents, a standard anesthetic technique was used for induction and maintenance of anesthesia (9). In the earlier study, Hodgkinson et al. (4) used a dose of less than 3 mg/kg of thiopental, and observed severe increases of MAP, pulmonary capillary wedge pressure, and pulmonary artery pressure during tracheal intubation. In one of the earliest studies, Kosaka et al. (10) found that maternal administration of large doses of thiopental (8 mg/kg) caused severe neonatal depression. Other investigators (11,12) showed that, in healthy parturients, although thiopental crossed the placenta with ease, an induction dose of 4 mg/kg was not associated with untoward neonatal effects. There are no studies documenting the safety and the effectiveness of the use of larger induction doses of thiopental (>4 mg/kg) in women with severe preeclampsia. Intravenous lidocaine may cause uterine vasoconstriction and uterine hypertonus and may further compromise the fetus in women with severe preeclampsia (13). Hence, intravenous lidocaine was not administered to patients in our study. The administration of narcotics may produce profound respiratory depression in the neonate. A vasodilator agent, such as nitroglycerine, or a combined α- and β-adrenergic blocking agent, such as labetalol, can be safely used to blunt the hypertensive response to tracheal intubation in women with severe preeclampsia (14,15). In our study, all patients in the GA group were pretreated with labetalol or nitroglycerine. As a result, their hemodynamic responses to tracheal intubation and surgical stimulation were significantly reduced. This is evident from the fact that although there were significant increases in MAP after tracheal intubation, these represented no significant change from baseline MAP.

Profound hypotension was an infrequent complication in the EA group. With induction of epidural anesthesia, MAP decreased from baseline values. However, this reduction was within 18%–20% from initial MAP and was not associated with adverse maternal or neonatal effects. Factors such as careful prehydration, close monitoring of central venous pressure or pulmonary capillary wedge pressure, maintenance of left uterine displacement, and slow induction of epidural blockade using local anesthetics in divided doses undoubtedly contributed to the stable hemodynamics in the EA group.

Neuroendocrine Responses

Both ACTH and β-endorphin-like immunoactivity increased significantly in the GA group at skin incision immediately after tracheal intubation. In the EA group, the concentrations of these hormones remained unchanged. Both ACTH and β-endorphin originate from a common precursor and are secreted by the pituitary in response to stress, acidosis, and hypoxia (16). During normal pregnancy, β-endorphin concentrations are similar to (16) or lower (17) than in nonpregnant controls. With the onset of labor, β-endorphin concentrations sharply increase and reach peak values during delivery and the immediate postpartum period (16–18). During labor, epidural analgesia decreases plasma β-endorphin concentrations (17). Similarly, ACTH concentrations increase in response to the stress of labor and reach peak values during delivery (19). In our study, none of the women were in active labor. The significant increase in concentrations of ACTH and β-endorphin immunoactivity in the GA group was related to the stress of tracheal intubation followed by surgical incision under light general anesthesia. In contrast, there were no significant changes in the concentrations of these hormones in the EA group throughout the study period.

Several investigators have studied the basal sympathetic tone as measured by arterial and venous catecholamine concentrations in women with preeclampsia, and the results are conflicting. For example, Davey et al. (20) and Oian et al. (21) reported that both epinephrine and norepinephrine concentrations were significantly higher in women with preeclampsia compared with normotensive pregnant women. On the other hand, Pedersen et al. (22) found that the concentrations of these hormones were similar in women with preeclampsia, those with essential hypertension, and normotensive pregnant control subjects. Nisell and colleagues (23) reported increased arterial epinephrine concentrations at rest and under stress, whereas the norepinephrine concentrations were normal both under basal conditions and during stress tests in women with preeclampsia. Zuspan and colleagues (24) noted that the 24-h urinary excretion of catecholamines was significantly higher in women with preeclampsia compared with controls. Nisell et al. (23) postulates that the sympathoadrenal responses in preeclampsia are similar to those observed in the nonpregnant state, implying inadequate adaptation of autonomic nervous system to pregnancy in women with preeclampsia. During labor, preeclamptic women have higher circulating levels of epinephrine and norepinephrine compared with normotensive controls, and epidural analgesia is followed by significant decreases in plasma concentrations of catecholamines (5). In our study, none of the patients were in active labor, and the basal concentrations of catecholamines were comparable to those previously reported. However, laryngoscopy and tracheal intubation caused dramatic and persistent increases in the levels of circulating catecholamines. In the EA group, the levels of these hormones decreased or remained remarkably constant throughout the study period.

Plasma cortisol concentrations increase during surgical stress; the magnitude of increase is related to the severity of the surgical stress, with highest levels occurring on emergence from anesthesia (25). In normal pregnancy, cortisol concentrations increase steadily, with peak levels occurring during labor and delivery (26). Epidural analgesia during labor causes a moderate decrease in the cortisol concentrations (27). Earlier reports of healthy normotensive women undergoing cesarean section show that cortisol concentrations increase significantly in those receiving general anesthesia, whereas they remain unchanged in patients receiving epidural block (3,28). In our patients, cortisol concentrations were significantly increased from baseline values only in the postpartum period. The reasons for the difference between our findings and those of others (3,28) are not entirely clear. In the GA group, the increased concentrations of cortisol in the postpartum period may be related to emergence from general anesthesia and in the EA group due to receding epidural block at the end of surgery.

Neonatal Outcome

The transient depression noted in babies in the GA group, as evidenced by the lower 1-min Apgar scores, may be related to the placental transfer of anesthetic drugs (2). In the GA group, although the umbilical pH and base deficit values were within the acceptable range, the base deficit was significantly larger compared with the EA group. Placental insufficiency is frequently present in severe preeclampsia (24), and the larger base deficit in infants in the GA group may be partly due to the increased maternal plasma catecholamine concentrations, causing further compromise of the uteroplacental perfusion (24,29). Maternal base deficit values were within normal limits. Similar to previous findings, neonatal hormone concentrations in our study showed no significant correlation with those in the mother (1,3). The mean β-endorphin-like immunoactivity tended to be more in the babies in the GA group compared with the EA group. Concentrations of other hormones were similar in the GA and EA groups. Thus, in our study, anesthetic technique did not influence neonatal stress hormone concentrations, probably owing to the small sample size and wide individual variations in the hormone concentrations in the neonates. However, there was significant correlation between ACTH and β-endorphin-like immunoactivity in the neonates, and we agree with others that these hormones may be partly secreted by the fetal pituitary (30). The significant negative correlations between β-endorphin-like immunoactivity and umbilical pH and Po_2 at delivery show that the concentrations of these hormones in the neonates increase in response to the stress of hypoxia and acidosis (30).

Our results have several important clinical implications. It is well known that the uteroplacental perfusion is decreased in women with severe preeclampsia. Further reduction of uterine artery blood flow is deleterious whether it is caused by hypotension during epidural anesthesia or by severe increases in catecholamine concentrations during general anesthesia. In agreement with earlier studies (31,32), our data show that profound hypotension is an infrequent complication with well-conducted epidural anesthesia. If hypotension does occur, it is easily treated. On the other hand, there are no techniques of proven safety in parturients, especially in those with severe preeclampsia, for prevention of the sudden and large increases in the catecholamine concentrations and other stress-related hormones in response to tracheal intubation and surgical stimulation during light general anesthesia. Hence, withholding epidural anesthesia from all severely preeclamptic women based on some of the earlier recommendations (7,8) is unwarranted. However, during the administration of epidural block, it is important to adhere to meticulous techniques involving close monitoring of maternal hemodynamic status, adequate prehydration, slow induction of the block with incremental doses of local anesthetics, and maintenance of left uterine displacement.

The long-term effects of anesthetic modification of maternal stress responses to cesarean delivery in terms of the incidence of maternal postoperative complications and perinatal morbidity and mortality are not known. Further retrospective and prospective studies in a large number of women with severe preeclampsia are required. In summary, our results indicate that in women with severe preeclampsia, epidural anesthesia extending to the fourth thoracic dermatome level causes blunting of the maternal hemodynamic and neuroendocrine stress response to cesarean delivery. The anesthetic technique did not alter the neonatal stress hormone concentrations.

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Epidural Anesthesia With 0.5% Bupivacaine: Influence of Age on Sensory and Motor Blockade

P-A. Nydahl, MD, PhD, L. Philipson, PhD, K. Axelsson, MD, PhD, and J-E. Johansson, MD

Departments of Anesthesiology and Intensive Care, Neurophysiology and Urology, Örebro Medical Center Hospital, Örebro, and the Department of Anesthesiology, Linköping University, Linköping, Sweden

To determine the influence of age on epidural blockade, 10 elderly male patients (mean age, 73 yr) and 11 young male volunteers (mean age, 25 yr) received epidural anesthesia with 20 mL of 0.5% bupivacaine with epinephrine at the L2-3 interspace. Median cephalad analgesia level (pinprick) was T-4 in the elderly and T-10 in the young subjects ($P < 0.01$). The duration of analgesia at the L-1 to S-3 segments was about 60 min shorter in the older patients than in the young volunteers ($P < 0.05$). Motor blockade was evaluated quantitatively by isometric muscle force measurements in the lower extremities and by electromyographic recordings from the abdominal and quadriceps muscles. Motor blockade in the lower extremities was also assessed qualitatively by the Bromage scale. The intensity of motor blockade was not influenced by age. The mean duration of maximal motor blockade of the lower abdominal muscles was 69 min in elderly patients and 140 min in young subjects ($P < 0.05$). The corresponding mean duration in the lower extremities was approximately 1.5 h in the older patients and 3 h in the young subjects ($P < 0.01$). The elderly patients could be mobilized 2 h earlier than the young volunteers. Duration of Bromage grade 1 was about 1.5 h shorter in the elderly than in the young subjects ($P < 0.01$). Not until 1.5–2 h after attainment of Bromage grade 0 was the muscle force in the lower extremities restored to 90% of baseline value. The authors conclude that cephalad spread was more extensive and duration of epidural blockade was shorter in elderly patients versus younger volunteers.

(Anesth Analg 1991;73:780–6)

The influence of age on the spread of local anesthetic solutions in epidural anesthesia has been studied extensively (1–10). On the one hand, injection of fixed volumes of local anesthetics epidurally provides more extensive spread of analgesia with increasing age (2,6,7,9,10). This has been confirmed in the age range 20–40 yr, but not in older subjects (3,5,7). Yet, other authors state that age is of little or no importance in the spread of epidural analgesia (4,8,11). Additional reports indicate that the profundity and duration of this blockade are not related to age (6,9,10). In these studies the motor blockade was assessed by the Bromage scale (12), which is qualitative and limited to the lower limbs. We, therefore, investigated the influence of age on motor blockade in epidural anesthesia as assessed by quantitative methods. We compared young subjects and elderly patients with respect to analgesia (pinprick) and to motor blockade during epidural anesthesia. The motor blockade was assessed by two quantitative methods, isometric muscle force measurements and electromyography (EMG), and by a qualitative method—the Bromage scale.

Methods

The study was approved by the Ethics Committee of the Örebro Medical Center Hospital, and informed consent was obtained from the patients and volunteers.

Ten male patients (ASA physical status I–II) aged 63–78 yr, scheduled for transurethral cystoscopy for a follow-up biopsy and/or minor resection of carcinoma of the bladder, entered the study. There were no patients with diabetes or neurologic disease. This group of 10 patients was compared with a group of 11 young male volunteers. Nine of these had undergone the investigations in a previous study (13). To increase the number of subjects in the young group, two young volunteers were added to the initial group of nine and were examined during the same period of time as the elderly patients. The ages of the 11

This study was supported by grants from the Örebro County Council.

Accepted for publication August 1, 1991.

Address correspondence to Dr. Nydahl, Department of Anesthesiology and Intensive Care, Örebro Medical Center Hospital, S-701 85 Örebro, Sweden.

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0003-2999/91/$3.50

Table 1. Patient Characteristics

Subjects	Age (yr)	Height (cm)	Weight (kg)
Young	25 ± 2.1	177 ± 1.9	74 ± 2.7
(*n* = 11)	(19–36)	(168–188)	(62–93)
Old	73 ± 1.7	172 ± 1.4	76 ± 2.1
(*n* = 10)	(63–78)	(165–180)	(70–93)

Values are mean ± SEM (range).

volunteers ranged from 19–36 yr. The heights and weights of the subjects in the two groups did not differ significantly (Table 1).

The epidural technique was the same in both age groups. Before the epidural injection, a rapid infusion of 500 mL of lactated Ringer's solution was given. All subjects received atropine, 0.25 mg IV, and the elderly patients were also given ephedrine, 25 mg IM. No other premedication or sedatives were administered. Epidural injection was made at the L2-3 interspace with the subject in the right lateral position. The epidural space was identified by the loss of resistance (1–2 mL of saline) technique with a 16-gauge Tuohy needle, with the bevel directed cephalad. Bupivacaine (0.5%) with epinephrine, 20 mL, was injected epidurally (4 mL as a test dose followed 2 min later by the remaining 16 mL at a rate of 1 mL/s). Immediately after the epidural injection, all the subjects were placed in the horizontal lithotomy position. During the following hour, another 300–500 mL of lactated Ringer's solution was infused. Ephedrine was given in a dose of 5 mg IV if the systolic blood pressure decreased by more than 30% of the initial value or if it decreased below 90 mm Hg.

With the subject in the lithotomy and horizontal position, bilateral measurements (sets of tests) were performed before epidural anesthesia and during its onset and regression. A set of tests consisted of, in sequence, bilateral determination of pinprick analgesia, maximal isometric muscle force of knee extension and EMG recordings from the quadriceps muscle during knee extension, isometric muscle force of hip flexion and of plantar flexion of the big toe, and EMG recordings from the rectus abdominis muscles. Thereafter, with the subject in the supine, horizontal position, assessments were made according to a modified four-grade Bromage scale (0–3) (0 = no paralysis [full flexion of knees and feet], 1 = just able to move the knees, 2 = able to move the feet only, 3 = total paralysis).

The maximal isometric muscle forces of knee extension, hip flexion, and plantar flexion of the big toe were recorded by force transducers. Each movement was performed five times in a set of tests and the mean value for each movement was calculated. Electromyographic activity was recorded by means of pairs of electrodes placed bilaterally over the rectus abdominis muscles, corresponding to skin dermatomes T-7, T-9, and T-11, and over the quadriceps muscle. For determining the isometric muscle force, EMG recordings were made from the quadriceps muscle during a 4-s-long maximal voluntary isometric muscle contraction produced by one of the five knee extensions and from the abdominal muscles at a trunk flexion of 5°–10° against a strap fixed over the chest. The EMG signals were fed into an eight-channel amplifier (van Gogh EP-8c) with a frequency range of 5–1000 Hz, digitized at a sampling rate of 3750 Hz/channel, processed, and stored in a computer. Electromyographic activity was presented as the mean value of the rectified EMG amplitude (RIEMG) over 1 s. The mean value represented three 1-s-long samplings during each muscle contraction. The methods of isometric force measurements and EMG recordings have been described in detail elsewhere (14,15).

A set of tests was performed four times within 60 min before the epidural injection. The mean preepidural values of the isometric muscle force for knee extension/hip flexion/plantar flexion of the big toe, and EMG values for abdominal and quadriceps muscles, were set at 100% (baseline values). The first recording of pinprick analgesia was made 5 min after epidural injection. During the onset phase, within the first hour, a set of tests was performed four times by the elderly patients and five times by the young subjects. When the elderly patients had attained the maximal degree of motor blockade, quantitative motor blockade measurements were discontinued for 45–60 min for surgical procedures. During the regression phase, measurements were made every 30–45 min in both groups. Measurements were made until pinprick analgesia had disappeared from the last segment and when the isometric muscle force at all measurement sites (hip, knee, toe) had regained 90% of the preepidural baseline values, i.e., when "complete regression of motor blockade" had been attained (Figure 1). A comparison of the course of the motor blockade, in terms of quantitative measurements, between the young and old groups was possible except for a short period of 45–60 min, i.e., during the surgical procedure in the elderly patients. Recording of analgesia and qualitative assessment of motor blockade (Bromage scale) could be performed without interruption.

Interpolation was made between the individually measured values, expressed as a percent of the baseline value, during the onset and regression of epidural anesthesia. Electromyographic values and isometric muscle force were also calculated at certain times after epidural injection. During onset and regression, the times at which the EMG and isometric force values amounted to 90%, 75%, 50%, 25%, 10%, and

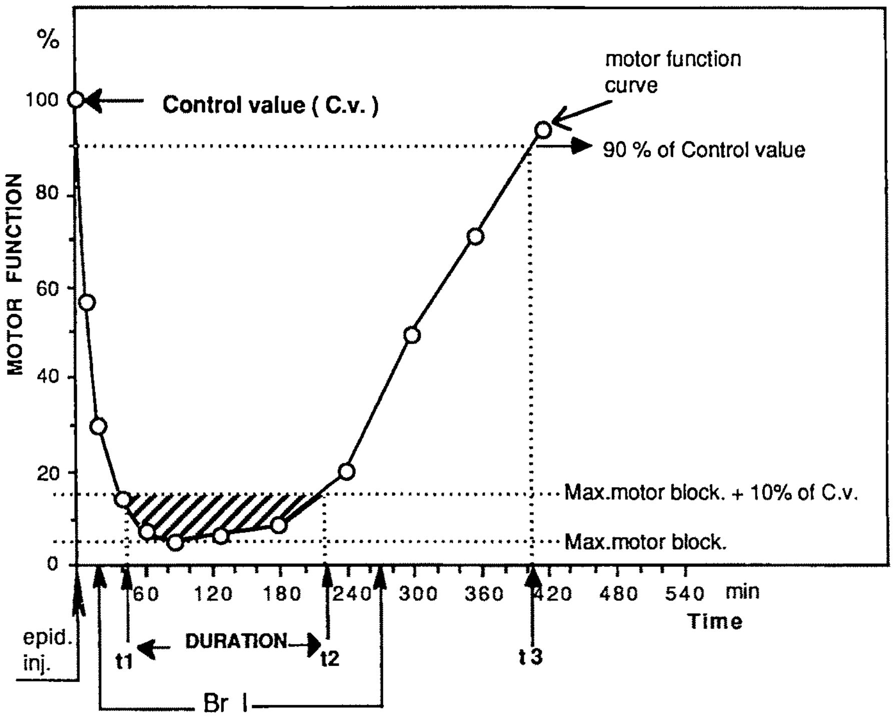

Figure 1. t_1 = Onset of maximal motor blockade. Duration of maximal motor blockade for each muscle group was estimated as the difference between the two calculated times t_1 and t_2. Complete regression of isometric muscle force or RIEMG = t_3 (at 90% of control value). Br 1 = duration of Bromage grade 1.

5% of the preepidural values were estimated. The duration of maximal motor blockade was recorded as the difference between the two calculated times t_1 and t_2 for each muscle group as shown in Figure 1.

The subject was mobilized when 90% of the preepidural isometric muscle force in the lower extremities was regained during the regression phase, and mobilization was tested in terms of the patient's ability to stand on his toes, raise himself from the sitting position, walk, and run.

The Mann-Whitney U-test was used to test for differences between young and old subjects and between two variables within a group, except for the degree of Bromage scale where Fisher's exact test was used. If more than two parameters were compared within a group, e.g., isometric muscle force of the knee, hip, and big toe or EMG values from dermatomes T-7, T-9, and T-11 and the quadriceps muscle, Kruskal-Wallis analysis of variance was applied to test for differences. Linear regression analysis was carried out to analyze the influence of age on the spread of analgesia and on the duration of the motor blockade. $P \leq 0.05$ was adopted as the level of statistical significance.

Results

The surgical procedures were well tolerated by the elderly patients. The median maximal cephalad spread of analgesia was at T-4 in the old patients and six segments more caudally (T-10) in the young subjects ($P < 0.01$). In the L-1 to S-3 segments, the mean durations were 224–260 min (range) in the elderly patients and 270–331 min in the young subjects, i.e., a difference of 46–71 min ($P < 0.05$). In the thoracic and the S4-5 segments, the difference between the groups regarding the duration of analgesia was not significant.

The results of the isometric muscle force measurements showed that the onset time of maximal motor blockade (t_1, Figure 1) did not differ significantly with respect to hip flexion, knee extension, and big toe flexion between the old (33–42 min) and the young subjects (40–53 min). The mean minimal isometric force values, expressed as a percent of the baseline value, were as follows: knee extension, 12%/7% (old/young, NS); hip flexion, 17%/14% (old/young, NS); and plantar flexion of the big toe, 31% (both old and young, Figure 2). The maximal intensity of motor blockade was thus significantly greater for knee extension and hip flexion than for flexion of the big toe, irrespective of age group ($P < 0.01$). The duration of maximal motor blockade in the lower limbs was 70–100 min shorter in the older patients than in the younger subjects ($P < 0.01$). Complete regression of the muscle force (90% of baseline value) at the different measurement sites (hip, knee, toe) occurred at about the same time both within the old and within the younger group (Figure 3). However, in the elderly patients the muscle force was regained 2 h earlier than in the young subjects ($P < 0.01$, Table 2).

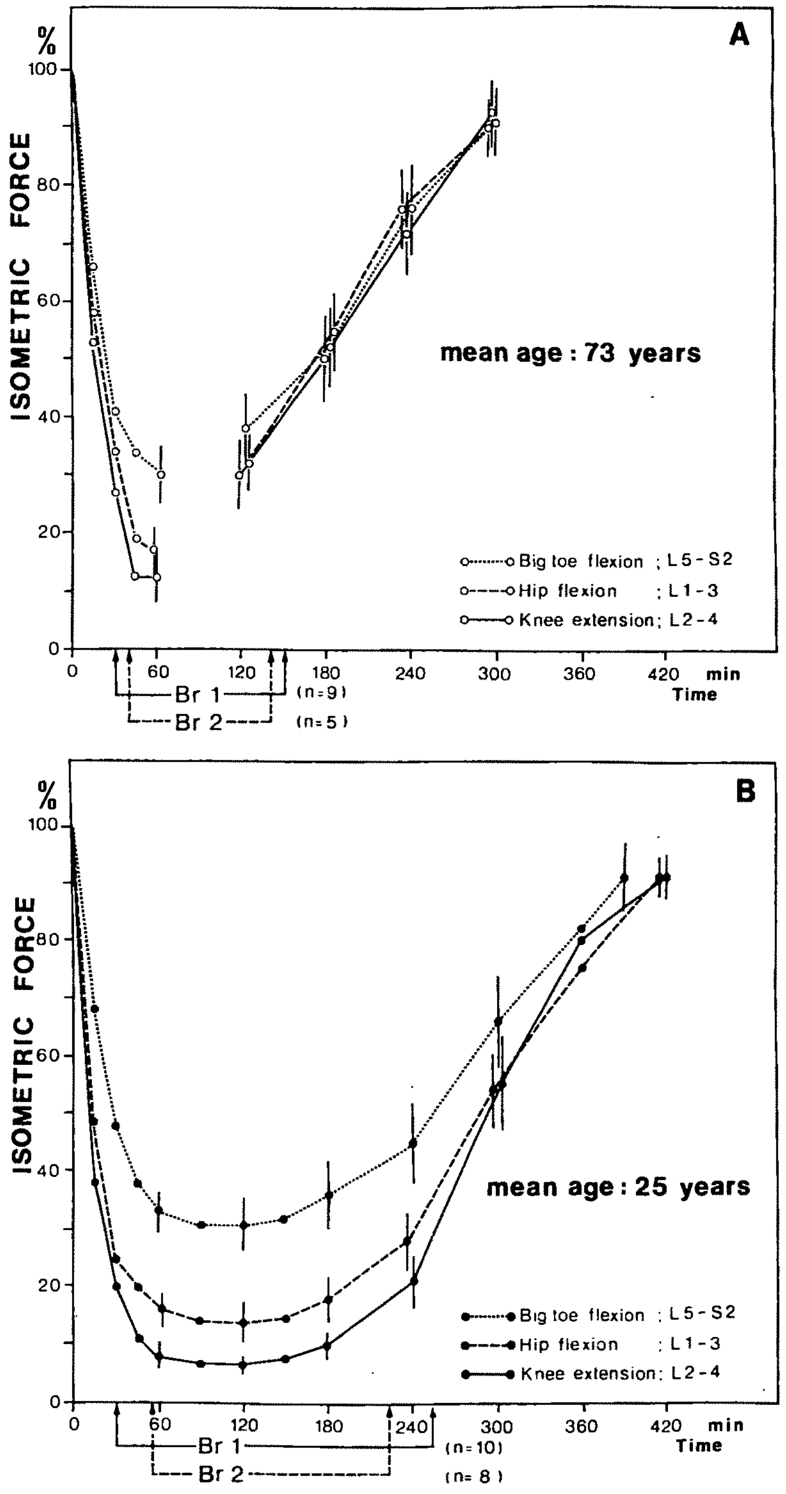

Figure 2. Onset and regression of motor blockade (mean ± SEM) in the lower extremities during epidural anesthesia with 20 mL of 0.5% bupivacaine with epinephrine. None of the contraction types (hip/knee/toe) showed complete motor blockade, but they started to return to and regained 90% of the control values at roughly the same time. The maximal intensity of motor blockade did not differ significantly between the two age groups (**A** and **B**). The duration of maximal motor blockade was shorter and complete regression was attained earlier in the elderly subjects (**A**) than in the young ones (**B**).

The mean onset time of grade 1 of the Bromage scale was the same in both groups (30 min after epidural injection in older patients and 31 min in young subjects). According to the Bromage scale, one subject in each age group had no motor blockade (grade 0) and one subject in each age group had complete motor blockade (grade 3). Although 7 of 11 young subjects had almost complete motor blockade (grade 2) compared with 4 of 10 elderly patients, the difference was not statistically significant. The Bromage scale returned to grade 0 about 2 h earlier in the elderly patients than in the young volunteers ($P <$

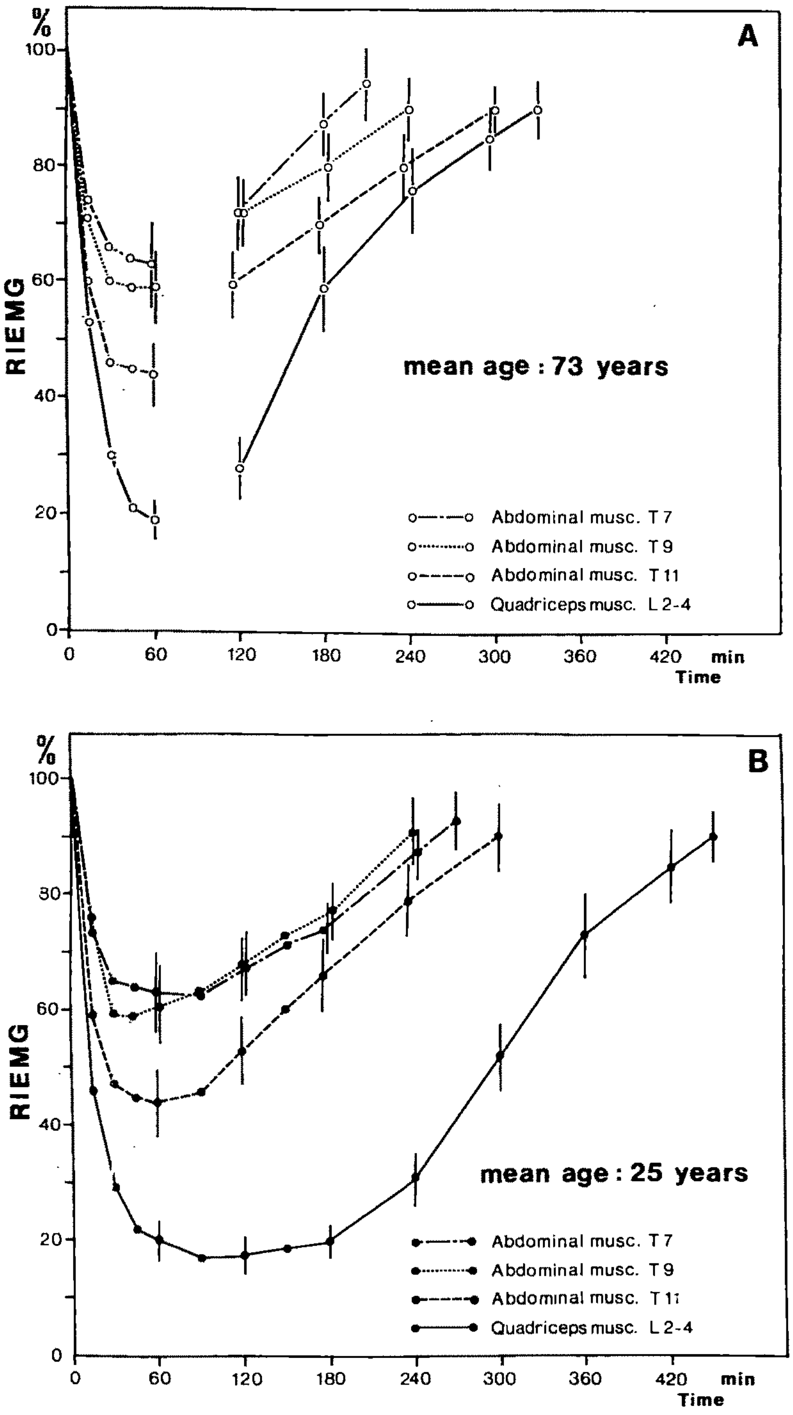

Figure 3. Onset and regression of motor blockade (mean ± SEM) during epidural anesthesia as a percent of the control value (100%) as estimated by RIEMG recorded from the rectus abdominis muscles at three levels and from the quadriceps muscle. In measurements from the lower part of the abdomen (T-11) and from the quadriceps muscle, groups A (elderly patients) and B (young volunteers) differed only in the duration of maximal blockade (see Figure 1). Complete regression in the quadriceps muscle occurred significantly later in the young group (B).

0.01, Table 2). In both age groups, however, the Bromage scale was restored 100–115 min earlier than when the isometric muscle force had regained 90% of the control value ($P < 0.01$, Table 2 and Figure 2).

The RIEMG recordings from the quadriceps muscles reflected the motor blockade in the same way as the isometric muscle force of knee extension (Figures 2 and 3).

The onset of maximal motor blockade (Figure 1) in the abdominal muscles occurred, on average, 28 min at T-7 and 40 min at T-11 after epidural injection in both age groups. The intensity of maximal motor blockade (lowest RIEMG value) did not differ statistically between the two age groups. At the T-7 and T-9 levels, it was 59%–63% of the baseline value and at the T-11 level, 44% (Figure 3). The difference in the

Table 2. Duration of Sensory and Motor Blockade in the Lower Extremities During Epidural Anesthesia[a]

	Young (min)	Old (min)
Sensory blockade		
Regression L2-4	329 ± 14.4	245 ± 18.8[b]
Motor blockade		
Isometric muscle force		
Knee extension (L2-4)		
Duration of maximal block[c]	188 ± 14.2	89.0 ± 14.4[b]
Complete regression	375 ± 21.8	248 ± 17.8[b]
Bromage scale[d]		
Grade 1 duration	226 ± 14.8	117 ± 22.8[b]
Grade 1 regression	260 ± 18.3	148 ± 21.5[b]

Values are mean ± SEM.

[a] Bupivacaine (20 mL of 0.5%) (L2-3).

[b] $P \leq 0.05$ (young vs old subjects).

[c] Duration of maximal brockade for each muscle group was estimated as the difference between the two calculated times t_1 and t_2.

[d] Complete regression of isometric muscle force = t_3 (at 90% of control value).

maximal intensity of motor blockade between the lower and upper part of the abdomen was not statistically significant. The mean duration of maximal motor blockade at the T-7 and T-9 levels (69–94 min) was about the same in the young as in the older group. In the lower part of the abdomen (T-11), the duration was 71 min longer in the younger subjects than in the older ones ($P < 0.05$). Complete regression of RIEMG (90% of baseline values) at the T7-11 levels was noted 169–212 min after the epidural injection in the elderly subjects and 207–249 min after the injection in the younger groups (not significant).

All subjects could be mobilized after the isometric force had become restored to 90% of the baseline levels. The young subjects could be mobilized, on average, 7.5 h (range 5–10.5 h) after the epidural injection and the older patients, 5.5 h (range 4–8 h) after the injection. However, 3 of 11 subjects in the young group and 3 of 10 in the older group complained of numbness in the feet; and 5 of 11 and 2 of 10, respectively, felt unstable when walking or running. Two subjects (one from each group) tended to stumble when running. One young subject had an atactic gait. These disorders vanished 30–45 min after mobilization.

There was a tendency within each age group for the spread of analgesia to be more extensive and for the motor blockade in the lower limbs to be of shorter duration with increasing age. But this tendency was statistically significant only in the young subjects (19–36 yr) ($P < 0.01$) and not in the older ones (63–78 yr) (linear regression analysis).

Arterial blood pressure remained stable in most of the subjects. One young volunteer was given atropine for bradycardia. Three patients in the older group received ephedrine, 5 mg IV, because of a decrease in blood pressure. The analgesic level in these four subjects was at T-4 or higher. The bradycardia and arterial blood pressure changes occurred within 40 min after epidural injection and were of short duration.

Discussion

There are only a few reports in the literature on the influence of age on the intensity and duration of motor blockade during epidural anesthesia. The present results indicate that the intensity of motor blockade, both caudal and cranial to the injection site, was not affected by the age of the subject, supporting earlier findings (6,9,10). In the present investigation, the motor blockade in the lower extremities was about 1.5 h shorter in duration in elderly than in young adults, irrespective of the method used to evaluate it. The correlation between duration of motor blockade and age was strongest in the group of young subjects (19–36 yr), and only in this group was it significant. In patients older than 63 yr, age was of no influence on the duration of motor blockade. Veering et al. (9) found no difference in the duration of motor blockade between two age groups when 0.5% bupivacaine without epinephrine was given epidurally. This discrepancy between their results and ours might be explained by the older mean age (36 yr) in their young group than in the present group of young subjects. The young subjects in the present study might have reacted more strongly to the epinephrine-containing solution than the older ones, resulting in more extensive vasoconstriction around the nerve tissues and a longer duration of sensory and motor blockade.

Another explanation for the shorter duration of analgesia and of motor blockade in the older subjects could be that the local anesthetic had access to a greater absorptive surface in the epidural space, as indicated by a wider spread of analgesia associated with a greater uptake of bupivacaine as a function of time. There are previous reports on higher and earlier peak plasma levels of lidocaine with aging after epidural injections of this agent (10,16). In contradiction, Veering et al. did not find a higher plasma concentration or a shorter correlated peak time of bupivacaine despite a more extensive spread of analgesia with age after epidural injection of plain bupivacaine (9). A more limited longitudinal distribution of local anesthetic within the epidural space, as in young persons, should give a greater mass of local anesthetic per unit nerve tissue, resulting in a more intense motor blockade; this was not found, however, in the young subjects of our study. It therefore seems that other factors are also involved. The larger intervertebral foramina in young subjects will imply greater leakage of local anesthetic, which will create greater opportunities for a segmental nerve blockade outside the epidural space in this group than in older patients (17). Such a segmental nerve blockade could have contributed to the longer duration of analgesia and motor blockade found in the young subjects of the present study (18).

Most anesthesiologists are familiar with the dose required in middle-aged and old patients. The result of injecting the same dose in young adults might be an unexpectedly inadequate spread of analgesia and prolonged motor blockade.

The Bromage scale only reflected the first half of the regression phase in the elderly patients, as has previously been found in young volunteers (19). The time required for complete regression of the motor blockade and the appropriate time of mobilization can only be estimated by quantitative isometric muscle force measurements and the RIEMG method. Both the quantitative and the qualitative methods illustrated that the duration of motor blockade was shorter in the older than in the young subjects.

In conclusion, the present study showed that the cephalad spread of analgesia was more extensive, whereas the duration of analgesia was about 1 h shorter, in elderly (63–78 yr) than in young persons (19–36 yr). The intensity of the motor blockade was equal in the two age groups tested, but the maximal motor blockade at the lower thoracic, lumbar, and upper sacral motor segments had a significantly shorter duration in the elderly patients, which meant that these patients could be mobilized 2 h before the young volunteers.

The valuable comments of Bertil Löfström, professor of anesthesiology, Linköping University, are greatly appreciated. The assistance of Ing-Marie Dimgren is gratefully acknowledged.

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Time Required for Oral Ranitidine to Decrease Gastric Fluid Acidity

Benjamin R. Jacobs, MD, Clyde A. Swift, MD, Herbert D. Dubow, MD,
Boonsri Kosarussavadi, MD, Kathryn McGoldrick, MD, Theresa Z. O'Connor, MPH,
and David G. Silverman, MD

Department of Anesthesiology, Yale University School of Medicine, Yale-New Haven Hospital, New Haven, Connecticut

This study documented gastric fluid acidity in ambulatory surgical patients 30–120 min after they had taken a 300-mg tablet of ranitidine, as changes specific to this relatively brief dose-to-sampling interval previously had not been delineated. At 20–120 min before outpatient surgery, ranitidine was given with 15 mL of water to 112 ASA physical status I–III adults without increased risk factors for aspiration of acidic gastric contents. After induction of general endotracheal anesthesia, the gastric fluid was aspirated. Volume and pH were compared with a reference group (pH = 1.6 ± 1; n = 161) that did not receive an H_2-antagonist or water. Of 40 patients sampled at 30–60 min after dosing, 26 had pH ≥2.5; mean pH was 3.9 ± 2 ($P < 0.05$ vs reference by Wilcoxon signed rank and χ^2 tests). Beyond 90 min, 28 of 28 patients had a pH ≥2.5, with a mean of 6.3 ± 1. No significant differences were noted with respect to mean gastric volume. We conclude that in patients without additional risk factors, oral ranitidine consistently prevents acid production when it is administered more than 90 min before induction of anesthesia.

(Anesth Analg 1991;73:787–9)

The ambulatory surgical patient poses particular problems with respect to prophylaxis against aspiration of gastric contents, as traditional preoperative antacid regimens commonly involve dosing the night before surgery. Although all ambulatory surgical patients ideally would be interviewed at least 1 day preoperatively, this often is not logistically possible. Many adult patients scheduled for ambulatory surgery are first seen by a member of the anesthesia care team on the morning of their scheduled surgery. To be effective in this setting, an antacid regimen must have a rapid onset. Although intravenous administration of an H_2-receptor antagonist typically reduces gastric acidity within 45–60 min, in most ambulatory centers intravenous access is not established before entry into the operating room. This has prompted evaluations of oral administration, an approach that offers the added advantage of being far less costly.

We have elected to evaluate orally administered ranitidine. Its onset is as fast as, or slightly faster than, comparable doses of cimetidine and famotidine in volunteers undergoing intermittent aspiration of gastric fluid (1). Previous investigations that sampled at 120 or 180 min (2,3) after oral dosing or that pooled data from samples obtained at 45–300 min (4–6) reported that ranitidine pretreatment resulted in gastric fluid with a mean pH ≥5.9 and a pH ≥2.5 in at least 90% of patients. Alternatively, sampling 60–120 min after administration of a 150-mg tablet obtained fluid with a pH >2.5 in only 25 of 30 (82%) patients (7). The present investigation was undertaken to document the changes in pH associated with oral administration of a 300-mg tablet 30–120 min before surgery.

Methods

With institutional review board approval, data were collected on ASA physical status I–III adults who underwent gastric aspiration during general endotracheal anesthesia for elective outpatient surgery. Of these, 112 patients received a 300-mg tablet of ranitidine (Zantac, Glaxo Inc.) with 15 mL of water on conclusion of the preoperative interview at 20–120 min before surgery. Each was without known gastrointestinal disease, asthma, systemic states that might affect gastro-

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Accepted for publication August 8, 1991.

Address correspondence to Dr. Silverman, Department of Anesthesiology, Yale University School of Medicine, Yale-New Haven Hospital, New Haven, CT 06510.

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0003-2999/91/$3.50

intestinal function (e.g., pregnancy, obesity, pain, or neurologic disorders), or concomitant use of medication known to influence gastric fluid acidity or volume. All patients enrolled for this investigation denied oral intake after midnight and received no other medications before surgery. There was no attempt to regulate the time interval between study drug administration and the onset of surgery; this was dependent on the operating room schedule. However, only those who received the ranitidine less than 120 min before surgery were included in analysis.

After induction of anesthesia with intravenous fentanyl (1–2 μg/kg), midazolam (0.02–0.05 mg/kg), thiopental (2–4 mg/kg), and vecuronium (0.05–0.1 mg/kg), the trachea was intubated. Anesthesia was maintained with oxygen, nitrous oxide, and either isoflurane or enflurane. Within 10 min of endotracheal intubation, an orogastric tube (18F Salem Sump) was passed. Its position was confirmed by auscultation of the epigastrium during insufflation of air. The stomach contents then were aspirated into a suction trap. Gastric fluid pH was determined to the nearest 0.5 pH units with commercial pH indicator strips (colorpHast; EM Science, Cherry Hill, N.J.); the pH of 10% of the samples also was confirmed by pH meter (Beckman model 3500, Irvine, Calif.). Volume was quantified to the nearest milliliter according to graduations on the suction trap.

A scattergram was generated to compare pH and the dose-to-sampling interval in all ranitidine-treated patients. In addition, the patients were grouped according to the following dose-to-sampling intervals: (a) 30–60 min, (b) 61–75 min, (c) 76–90 min, and (d) 91–120 min. (The two samples obtained between 20 and 30 min were excluded from this analysis.) Data at each interval were expressed as mean ± standard deviation and compared with a reference group of 161 patients who met inclusion criteria and underwent the same testing procedures but were not given ranitidine or water. The ranitidine and reference patients were compared using unpaired *t*-test and χ^2 analyses; $P < 0.05$ was considered to be statistically significant.

Results

The ability of ranitidine to progressively increase gastric fluid pH with increasing dose-to-sampling interval is illustrated in Figure 1. Patients treated with ranitidine exhibited a significant difference from the control group within 30–60 min after drug administration with respect to pH (3.9 ± 2 vs 1.6 ± 1) and incidence of pH ≥2.5 (26/40 vs 22/161). The pH increased over the ensuing dose-to-sampling intervals (Table 1): $P < 0.05$ for pH after a 30–60-min interval versus after each of the subsequent intervals; and $P < 0.05$ for incidence of pH ≥2.5 after 30–60 min versus after 91–120 min. Between 91 and 120 min, 28 of 28 patients had a pH ≥2.5, with a mean pH of 6.3 ± 1; the pH was ≥4.0 in all but one of the 28 samples.

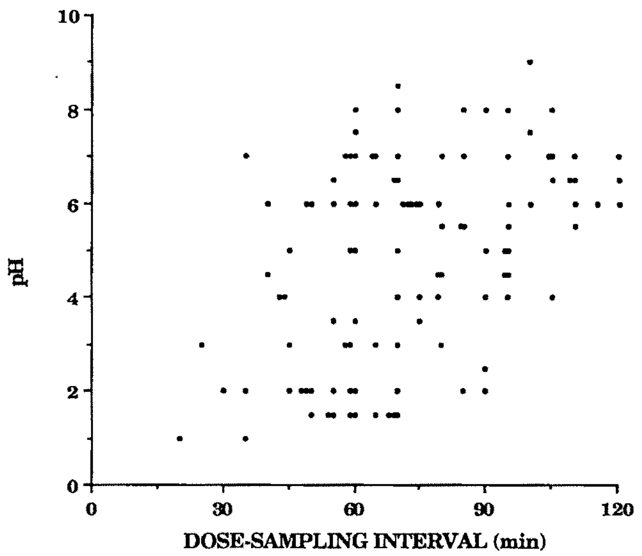

Figure 1. Scattergram of pH versus time after oral ranitidine administration for all cases in which sampling was performed within 120 min of dosing.

Table 1. Changes in pH With Time

	Time intervals (min)			
pH Values	30–60	61–75	76–90	91–120
Mean ± SD	3.9 ± 2	5.0 ± 2	5.3 ± 2	6.3 ± 1
Median (range)	3.5 (1–8)	6 (15–8.5)	5.5 (2–8)	6.5 (3–9)
No. with pH ≥2.5	26/40	20/25	15/17	28/28

No significant effect was noted with respect to gastric fluid volume. It averaged 21 ± 18 mL and 14 ± 14 mL in the control and ranitidine groups, respectively, and did not change markedly with the dose-to-sampling interval.

Discussion

Although pH and volume both influence the risk associated with pulmonary aspiration of gastric contents (8), recent evidence suggests that pH is more critical (9). In the present study population, oral administration of an H_2-antagonist effectively reduced gastric acidity in less than 120 min. Ranitidine, 300 mg PO, provided a pH ≥2.5 in 15 of the 17 patients who received the medication 76–90 min before sampling and in 28 of 28 who received it 91–120 min before sampling. These data are consistent with findings that the gastric fluid of 82% of patients pretreated with cimetidine 60–90 min before sampling had a pH >2.5 (10), and they expand upon previous assessments of ranitidine that did not delineate changes at such brief dose-to-sampling intervals (3–6).

It appears that oral administration achieves maximal effectiveness approximately 30–45 min slower than intravenous dosing (5,11), consistent with a progressive increase of plasma levels for several minutes after oral dosing (12). In the range of doses commonly used, plasma levels of H_2-antagonists are proportional to the dose administered (13). Thus, the "delay" associated with oral dosing may be overcome, in part, by increasing the dose or combining drugs. The potential benefit of higher dosing was not appreciated when a longer dose-to-sampling interval was used, prompting one group of investigators to conclude that there is no advantage to doubling the dose in healthy patients (6).

Consistent with other reports (10,14), ranitidine had an unreliable effect on gastric volume in the present study. This may be attributable, in part, to our sampling technique; dye dilution studies indicate that positioning of an orogastric tube by auscultation may lead to sampling that underestimates the actual gastric volume (15). Recent evidence suggests that any decrease in gastric volume resulting from oral H_2-antagonist therapy would not have been countered by the 15 mL of water given with the ranitidine tablet; gastric volume actually may be decreased 60–150 min after drinking clear liquid (16,17).

In conclusion, preoperative oral administration of ranitidine effectively decreases gastric fluid acidity if given to healthy patients more than 90 min before induction of anesthesia for outpatient surgery. It does not require an established intravenous route and typically costs 10%–20% of intravenous dosing. The present findings provide a basis for more extensive comparisons of orally administered agents. Higher doses of ranitidine and other H_2-antagonists should be evaluated, especially in the context of increased risk factors.

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Pharmacokinetics of Sufentanil in Obese Patients

Arthur E. Schwartz, MD, Richard S. Matteo, MD, Eugene Ornstein, PhD, MD,
William L. Young, MD, and Kelly J. Myers, BS

Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York

The pharmacokinetics of sufentanil were determined in eight obese (94.1 ± 14 kg, mean ± SD) and eight control patients (70.1 ± 13 kg) anesthetized for neurosurgery. After induction of anesthesia, 4 μg/kg of sufentanil was administered in a single intravenous bolus. Multiple arterial samples were obtained at timed intervals over 6 h, and plasma concentrations of sufentanil were measured by radioimmunoassay. Calculation of pharmacokinetic variables from the derived compartmental models demonstrated an increased volume of distribution of sufentanil in the obese (9098 ± 2793 mL/kg ideal body weight, mean ± SD) when compared with a control group (5073 ± 1673 mL/kg ideal body weight) ($P < 0.01$) and a prolonged elimination half-life (208 ± 82 min vs 135 ± 42 min, $P < 0.05$). The total volume of distribution correlated linearly with the degree of obesity, as expressed in percent ideal body weight ($r = 0.67$). In contrast, plasma clearance was similar in both obese and control groups (32.9 ± 12.5 vs 26.4 ± 5.7 mL/kg ideal body weight). The high lipid solubility of sufentanil probably explains the altered pharmacokinetics of this opioid in obese patients.

(Anesth Analg 1991;73:790–3)

Obesity is associated with anatomic and physiologic changes that may alter drug disposition. Obese individuals have an increased proportion of body fat to total body mass and a decreased proportion of muscle mass and body water (1,2). Furthermore, both cardiac output and intravascular volume are increased (3). For the lipophilic benzodiazepine diazepam, Abernathy et al. (4,5) demonstrated an increased volume of distribution with obesity. Similar findings were reported for oxazepam, lorazepam, and midazolam (6,7). In contrast, the volumes of distribution of cimetidine and digoxin are nearly independent of excess body mass (8,9).

The partition coefficient of sufentanil between *n*-octanol and water of 1754 indicates high lipid solubility (10). This prompted our investigation of sufentanil pharmacokinetics in obese surgical patients.

Methods

This study was approved by the Institutional Review Board of Columbia University, College of Physicians and Surgeons. Written informed consent to inclusion in the study was obtained from eight obese and eight control patients scheduled to undergo intracranial, spinal, or neurovascular surgery. Patients with clinical or laboratory evidence of cardiac, hepatic, or renal dysfunction were excluded.

Obese patients were at least 30% above ideal body weight (IBW), whereas control patients were within 10% of IBW. Ideal body weight was defined as follows (3,5–7):

$$\text{IBW (male)} = 49.9\text{ kg} + 0.89\text{ kg/cm above }152.4\text{ cm height},$$

$$\text{IBW (female)} = 45.4\text{ kg} + 0.89\text{ kg/cm above }152.4\text{ cm height}.$$

Percentage IBW was defined as the ratio of total body weight to IBW.

Oral diazepam (5–10 mg) was given approximately 2 h before scheduled operation. All subjects received metocurine (2 mg IV) before induction of anesthesia with thiopental (3–7 mg/kg IV), and tracheal intubation was facilitated with succinylcholine (1.5 mg/kg IV). Anesthesia was maintained with 66% nitrous oxide in oxygen. Additional metocurine was given for neuromuscular blockade. All patients received oxacillin (2 g IV) and dexamethasone (10 mg IV). Propranolol (1–4 mg) or hydralazine (10–20 mg) were administered for hypertension. Esophageal temperature was maintained at 35.3°–36.7°C with warming blankets. Ventilation was controlled to maintain end-tidal carbon dioxide tension between 27 and 32 mm Hg as

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Supported in part by Janssen Pharmaceutica, Inc.

Accepted for publication August 1, 1991.

Address correspondence to Dr. Schwartz, Neuroanesthesia Group—AP 901, Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, 161 Fort Washington Avenue, New York, NY 10032.

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0003-2999/91/$3.50

Table 1. Demographic Data

	Obese group (n = 8)	Control group (n = 8)	P
Age (yr)	52 ± 12	44 ± 11	NS
Height (cm)	167 ± 7	174 ± 9	NS
Sex (M/F)	2/6	3/5	NS
Weight (kg)	94.1 ± 14	70.1 ± 13	<0.01
IBW (kg)	59.9 ± 6.9	66.5 ± 9.5	NS
% IBW	159.4 ± 16.6	105.0 ± 5.0	<0.01

Values are mean ± SD.
NS, not significant; IBW, ideal body weight.

measured by infrared analysis. Sufentanil (4 μg/kg) (total body weight) was injected as an intravenous bolus. Blood samples were obtained from a radial artery cannula at 1, 3, 5, 10, 15, 30, 45, and 60 min and then at 30-min intervals to 360 min. Samples were heparinized and plasma was separated and frozen until assayed by radioimmunoassay (11). The assay had a sensitivity of 0.1 ng/mL and a coefficient of variation of 4.46%.

Both biexponential and triexponential equations were fitted for each patient to the plasma concentration decay curves using weighted nonlinear least-squares regression analysis (12). The weighting factor used was $1/C_t^2$ (where C_t is the sufentanil concentration at time t). The Boxenbaum method was used to determine whether a two- or three-compartment model provided the best fit (13). The coefficients and exponents of the equations defining the fitted curves for each patient were used to calculate the pharmacokinetic variables (14). The total volume of distribution was determined by the area method.

Volumes of distribution and clearances per kilogram of ideal body weight were determined by dividing volume of distribution (in milliliters) or clearance (in milliliters per minute) by IBW to permit meaningful comparisons between obese and control patients.

Comparisons of demographic data and pharmacokinetic values were made by the two-tailed t-test for unpaired data. Linear regression analysis was used to determine correlation between pharmacokinetic variables and percent IBW. $P < 0.05$ was considered significant.

Results

There were no significant differences between groups for age, sex, or height (Table 1). The weight of obese patients was 94.1 ± 14 kg (mean ± SD) (159.4% ± 16.6% IBW), whereas that of control patients was 70.1 ± 13 kg (105.0% ± 5.0% IBW).

The plasma concentration versus time curves for all patients were best described by biexponential equations. The pharmacokinetic data are presented in Tables 2 and 3. Obese patients had both a larger total volume of distribution of sufentanil and a longer elimination half-life as compared with control patients. Linear regression analysis showed a positive correlation between total volume of distribution and percent IBW ($r = 0.67$, $P < 0.05$) (Figure 1). There was no significant correlation between plasma clearance and percent IBW ($r = 0.38$). Elimination half-life

Table 2. Coefficients and Exponents of Fitted Curves

Patient	A (ng/mL)	α (min^{-1})	B (ng/mL)	β (min^{-1})
Control group				
1	3.56	0.193	0.624	0.0048
2	4.81	0.152	0.533	0.0035
3	4.02	0.181	0.937	0.0107
4	6.18	0.181	0.515	0.0044
5	6.99	0.135	0.964	0.0063
6	3.45	0.091	0.482	0.0045
7	3.80	0.108	0.572	0.0045
8	24.8	0.441	1.140	0.0071
Mean (SD)	7.20 (7.23)	0.185 (0.11)	0.721 (0.253)	0.0057 (0.0023)
Obese group				
1	2.64	0.077	0.562	0.0027
2	4.47	0.104	0.288	0.0042
3	6.80	0.071	0.367	0.0065
4	7.49	0.326	0.939	0.0048
5	4.45	0.139	0.516	0.0020
6	3.52	0.094	0.548	0.0025
7	3.43	0.080	0.431	0.0033
8	6.07	0.176	0.873	0.0045
Mean (SD)	4.86 (1.74)	0.133 (0.086)	0.566 (0.23)	0.0038 (0.0015)

Table 3. Pharmacokinetic Data

	Obese group (n = 8)	Control group (n = 8)	P
Initial volume of distribution (mL/kg)	815 ± 268	712 ± 286	NS
Initial volume of distribution/IBW (mL/kg)	1254 ± 326	745 ± 292	<0.01
Distribution half-life (min)	6.6 ± 2.7	4.6 ± 1.9	NS
Total volume of distribution (mL/kg)	5818 ± 1745	4818 ± 1515	NS
Total volume of distribution (L)	547 ± 178	346 ± 144	<0.05
Total volume of distribution/IBW (mL/kg)	9098 ± 2793	5073 ± 1673	<0.01
Plasma clearance (mL·min^{-1}·kg^{-1})	20.8 ± 7.3	25.2 ± 5.7	NS
Plasma clearance (L/min)	1.99 ± 0.86	1.78 ± 0.52	NS
Plasma clearance/IBW (mL·min^{-1}·kg^{-1})	32.9 ± 12.5	26.4 ± 5.7	NS
Elimination half-life (min)	208 ± 82	135 ± 42	<0.05

Values are mean ± SD.
IBW, ideal body weight.

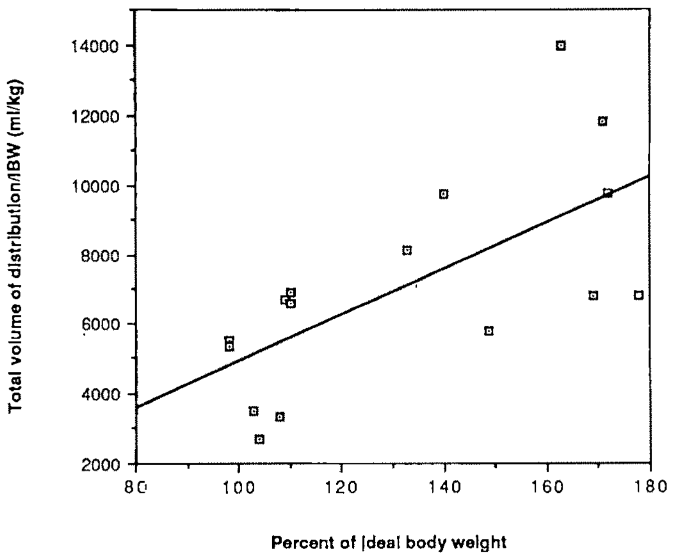

Figure 1. Relation of sufentanil total volume of distribution/ideal body weight to percent ideal body weight. *Solid line* was determined by linear regression analysis (r = 0.67).

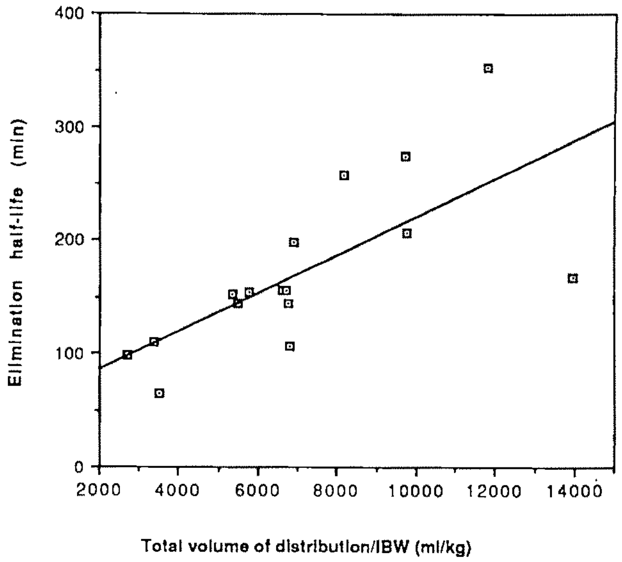

Figure 2. Relation of sufentanil elimination half-life to total volume of distribution/ideal body weight. *Solid line* was determined by linear regression analysis (r = 0.70).

correlated with total volume of distribution (Figure 2) (r = 0.70) but not with plasma clearance (r = 0.26).

Discussion

Our results indicate an increased total volume of distribution of sufentanil with obesity, resulting in a prolongation of the elimination half-life. Furthermore, the increased volume of distribution is correlated with the magnitude of obesity. This is consistent with the high lipid solubility of this opioid and with the increased proportion of fat tissue in these patients.

The values for volume of distribution, clearance, and elimination half-life of the control group in this study are similar to that of previously published reports. Bovill et al. (15) fitted two- or three-compartment models to plasma decay curves of sufentanil administered as a 5-μg/kg bolus to surgical patients also receiving enflurane or halothane. In earlier work from our group and in the present study, sufentanil concentration versus time data were best described by two-compartment models (16,17). This agrees with the results of Davis et al. (18) who reported on sufentanil pharmacokinetics in children. Anesthetic technique, magnitude of blood loss, and site or duration of sampling may determine whether a two- or three-compartment model best describes sufentanil pharmacokinetics.

The duration of blood sampling in our study was 6 h, two to three times the elimination half-life of sufentanil for our control patients (135 ± 42 min). This is similar to the elimination half-life of 164 ± 22 min reported by Bovill et al. after 8 h of sampling.

It is similar also to the value derived by Chauvin and colleagues (19) for control patients (210 ± 54 min) in which blood sampling extended to 10 h. These values contrast sharply with the 12.1 ± 5.8 h elimination half-life reported for patients undergoing abdominal aortic surgery, in which sufentanil was measured up to 24 h after infusion (20). Duration of sampling may account for the difference. However, the aortic surgery patients represented an older, chronically ill group. Furthermore, their anesthetic regimen included unspecified vasoactive drugs, autotransfusion of salvaged blood, infrarenal aortic cross-clamping with probable reduction in hepatic blood flow, and infusion of large volumes of crystalloids with expected decreases in drug binding and increases in drug distribution.

The limitation of blood sampling time to 6 h in the present study may indicate that our value of 208 ± 82 min may underestimate the prolonged elimination half-life of sufentanil in the obese group, as extending duration of sampling may lead to larger estimates of elimination half-life (21). However, plasma concentrations of sufentanil beyond 6 h were at the limits of sensitivity of our assay, and increased doses of sufentanil beyond 4 μg/kg resulted in excessive opioid effects beyond the duration of the operation.

The similar volumes of distribution of sufentanil when expressed in milliliters per kilogram in obese and control patients suggest that the drug is distributed at least as extensively in the excess body mass as lean body mass. This indicates that loading doses to achieve predetermined plasma concentrations must account for total body mass. However, the slow elimination of sufentanil in the obese patient suggests that infusion or maintenance doses must be prudently reduced. This is particularly important in view of the known increased risk of postoperative hypoxemia in the obese (22).

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Dose Requirements of Vecuronium, Pancuronium, and Atracurium During Orthotopic Liver Transplantation

Breda O'Kelly, FFARCSI, Pascal Jayais, MD, Phillipe Veroli, MD, Cécile Lhuissier, MD, and Claude Ecoffey, MD

Département d'Anesthésie-Réanimation, Hôpital Paul Brousse, Université Paris-Sud, Villejuif, France

To further elucidate the role of the liver in the clearance of vecuronium, atracurium, and pancuronium, 30 patients undergoing orthotopic liver transplantation were randomly assigned to three comparable groups to receive a continuous infusion of vecuronium, atracurium, or pancuronium. The evoked integrated compound action potential of the hypothenar eminence in response to train-of-four ulnar nerve stimulation was measured and recorded. Anesthesia was induced with 3–5 mg/kg of thiopental, 50 μg/kg of midazolam, and 1–5 μg/kg of fentanyl IV and was maintained with continuous infusions of midazolam and fentanyl while the lungs were ventilated with an air-oxygen mixture. The infusion rates of vecuronium, atracurium, and pancuronium were adjusted to achieve a T1/Tc ratio of between 0.02 and 0.10 (T1 = height of first twitch, Tc = height of control twitch). Vecuronium and pancuronium requirements, which were 0.072 ± 0.022 and 0.042 ± 0.015 $mg \cdot kg^{-1} \cdot h^{-1}$ (mean ± standard deviation) respectively during the dissection phase, decreased significantly during the anhepatic phase to 0.036 ± 0.021 and 0.018 ± 0.012 $mg \cdot kg^{-1} \cdot h^{-1}$ and returned toward the initial values in the postreperfusion phase (0.055 ± 0.018 and 0.032 ± 0.012 $mg \cdot kg \cdot^{-1} \cdot h^{-1}$); whereas atracurium requirements remained unchanged during the three phases (0.667 ± 0.199, 0.567 ± 0.142, and 0.692 ± 0.254 $mg \cdot kg^{-1} \cdot h^{-1}$). These data suggest that the liver has an important role in the elimination of vecuronium and pancuronium, whereas the elimination of atracurium is unaltered during exclusion of the liver from the circulation.

(Anesth Analg 1991;73:794–8)

The role of the liver in the pharmacokinetics and pharmacodynamics of vecuronium, atracurium, and pancuronium is different for each of these three drugs. The clearance of vecuronium in patients with hepatic cirrhosis varies with the dose injected. Clearance decreases after a relatively large dose (i.e., 0.2 mg/kg) but remains unaltered after the administration of 0.1 mg/kg (1,2). Both a decrease in the plasma clearance and a marked increase in the volume of distribution of pancuronium have been described (3). On the other hand, impaired liver function does not alter either atracurium's elimination or plasma clearance (4,5). Monitoring the integrated compound action potential of the hypothenar eminence evoked by supramaximal stimulation of the ulnar nerve (6) allows a similar degree of blockade to be achieved by changing the rates of infusion of a neuromuscular blocking drug. The exclusion of the hepatic circulation and function during the anhepatic phase of orthotopic liver transplantation (OLT) did not alter requirements of atracurium significantly in humans (7). Similar information concerning vecuronium and pancuronium is not available. We therefore undertook a study comparing the requirement of vecuronium, pancuronium, and atracurium throughout OLT in humans.

Methods

After approval by our Institutional Ethics Committee, 30 adult patients who required OLT were studied. They were randomly assigned to three groups of 10 patients each to receive vecuronium, atracurium, or pancuronium as the only neuromuscular blocking drug during surgery. Their characteristics, liver pathology, and the results of liver and renal function tests performed preoperatively are shown in Table 1.

All 30 patients were orally given 100 mg of hydroxyzine 90 min before induction of anesthesia. After breathing oxygen for 5 min, anesthesia was intravenously induced with 3–5 mg/kg of thiopental, 50 μg/kg of midazolam, and 1–5 μg/kg of fentanyl. To

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Presented in part at the meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 1990.

Accepted for publication August 13, 1991.

Address correspondence to Dr. Ecoffey, Département d'Anesthésie-Réanimation, Hôpital de Bicêtre, 94275 Kremlin-Bicêtre Cedex, France.

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0003-2999/91/$3.50

Table 1. Preoperative Data

	Vecuronium	Atracurium	Pancuronium
n	10	10	10
Age (yr)	42 ± 7	49 ± 7	46 ± 11
Weight (kg)	63 ± 6	66 ± 14	60 ± 9
Sex ratio (M/F)	6/4	5/5	4/6
Liver pathology			
Cirrhosis	6	9	9
Sclerosing cholangitis	1		1
Liver tumor	1		
Retransplantation	1	1	
Acute fulminant hepatitis	1		
Clotting factor V			
Preoperative value (%)	23 ± 13	34 ± 11	37 ± 19
Creatinine			
Preoperative value (mmol/L)	82 ± 38	84 ± 18	79 ± 24

Values are mean ± SD.

facilitate tracheal intubation, 0.1 mg/kg of vecuronium, 0.6 mg/kg of atracurium, 0.1 mg/kg of pancuronium was administered once a stable recording had been achieved on the neuromuscular transmission analyzer (Datex Relaxograph). Ventilation was controlled with a warmed humidified oxygen/air mixture, and minute volume was adjusted to maintain an end-tidal carbon dioxide tension ranging between 32 and 36 mm Hg. Anesthesia was maintained with a continuous infusion of fentanyl (10 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and midazolam (50 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Piperacillin (4 g) was given every 8 h as antibiotic prophylaxis, and 5 mg/kg of methylprednisolone and 1 mg/kg of azathioprine were given as the first part of the antirejection therapy. Blood loss was replaced with transfusions of packed red blood cells and fresh frozen plasma. All the usual monitoring for liver transplantation was used.

Orthotopic liver transplantation surgery is divided into three phases. The first phase consists of a dissection during which the inferior vena cava above and below the liver, the portal vein, the hepatic artery, and the common bile duct are isolated. This lasts for approximately 4 h. The anhepatic phase begins when the hepatic artery, portal vein, and inferior vena cava above and below the liver are cross-clamped. During this phase, which lasts over 1 h, the recipient's liver is removed and the inferior vena cava and portal vein are anastomosed with the donor's liver. The inferior vena cava and portal vein are then unclamped. In the third phase, the post-reperfusion stage, the hepatic artery and biliary duct anastomoses are performed.

Before injecting the neuromuscular blocking drug, five small disposable pregelled silver-silver chloride surface electrodes were applied to the skin that had been cleaned thoroughly with alcohol. The stimulating electrodes of the neuromuscular transmission analyzer (Datex Relaxograph) were applied over the ulnar nerve, and the recording electrodes were placed over the hypothenar eminence. Supramaximal train-of-four stimuli were delivered every 20 s. The evoked integrated compound action potential of the hypothenar eminence was recorded, and this response to the supramaximal stimulus is set as the 100% reference value (Tc). Once a stable recording had been achieved for 180 s, an intravenous bolus of vecuronium, atracurium, or pancuronium was injected to facilitate tracheal intubation. The height of the first twitch in the train-of-four with respect to the control twitch height (T1/Tc) was recorded continuously. When recovery from the initial bolus dose was evident by a single twitch depression (T1/Tc) of more than 0.05, an infusion of vecuronium, atracurium, or pancuronium was started. The initial rate of these infusions was 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ for vecuronium, 0.6 $mg \cdot kg^{-1} \cdot h^{-1}$ for atracurium, and 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ for pancuronium. The rate of these infusions was adjusted by an increase or decrease of 25% every 6–15 min to maintain T1/Tc between 0.02 and 0.10. This magnitude of neuromuscular blockade was required to facilitate surgery. In eight patients, spontaneous recovery of the control twitch tension was allowed at the end of the procedure where a return to the Tc level was observed, thus demonstrating stability of the system. The total dose of each drug given during each of the three phases was recorded. To calculate the requirements during a phase, the dose given during that phase was divided by the duration of that phase. The initial bolus dose given before tracheal intubation was excluded from the calculations. Thus, phase 1 requirements were calculated from the time the infusion was started until the start of the anhepatic phase.

Results are expressed as mean ± SD. Statistical analysis was performed using repeated measures of analysis of variance followed by Fisher's test ($P < 0.05$ was considered significant).

Results

Patients were similar in the three groups with respect to age, weight, liver pathology, and preoperative values of creatinine and clotting factor V (Table 1). In addition, the duration of each stage of OLT, temperature, pH, and red blood cell and fresh frozen plasma replacements were similar in the three groups (Table 2).

Vecuronium and pancuronium requirements, which were 0.072 ± 0.022 and 0.042 ± 0.015 $mg \cdot kg^{-1} \cdot$

Table 2. Intraoperative Data

	Dissection phase[a]			Anhepatic phase[a]			Postreperfusion phase[a]		
	Vecuronium	Atracurium	Pancuronium	Vecuronium	Atracurium	Pancuronium	Vecuronium	Atracurium	Pancuronium
Duration (min)	268 ± 55	259 ± 60	281 ± 103	78 ± 25	90 ± 29	106 ± 39	303 ± 62	321 ± 84	348 ± 114
Temperature (°C)	35.8 ± 0.7	35.7 ± 0.7	35.5 ± 0.6	35.8 ± 0.8	35.4 ± 1.0	35.5 ± 0.6	36.3 ± 0.6	36.4 ± 0.9	36.0 ± 1.0
pH (U)	7.47 ± 0.06	7.43 ± 0.07	7.46 ± 0.02	7.47 ± 0.06	7.44 ± 0.07	7.46 ± 0.07	7.40 ± 0.10	7.46 ± 0.06	7.44 ± 0.06
Red blood cells (U)	5.7 ± 3.4	6.2 ± 4.7	5.7 ± 4.6	1.7 ± 2.3	2.4 ± 2.4	1.5 ± 4.6	6.9 ± 6.4	10.4 ± 13.2	7.2 ± 7.5
Fresh frozen plasma (U)	11.4 ± 6.6	12.5 ± 8.1	12.3 ± 7.1	5.5 ± 3.5	6.2 ± 6.9	4.9 ± 3.6	14.7 ± 10.4	21.9 ± 19.2	13.4 ± 9.0

[a] Phase of orthotopic liver transplantation.

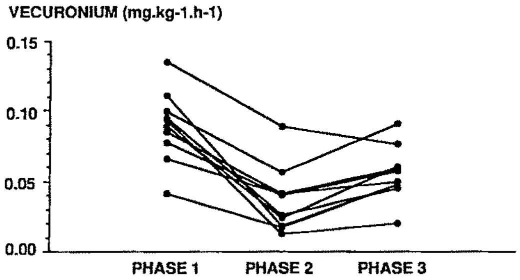

Figure 1. Individual change in vecuronium requirements during each phase (phase 1, the dissection phase; phase 2, the anhepatic phase; phase 3, the postreperfusion phase).

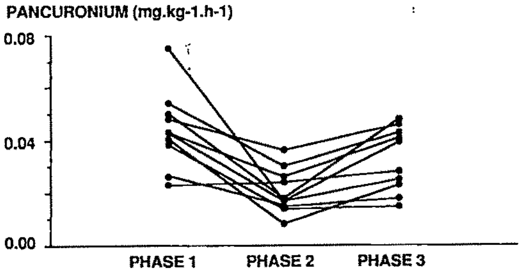

Figure 2. Individual changes in pancuronium requirments during each phase.

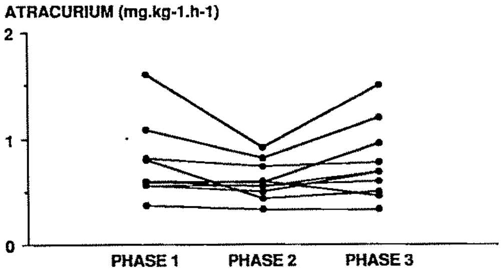

Figure 3. Individual changes in atracurium requirements during each phase.

h^{-1}, respectively, during the dissection phase, decreased significantly during the anhepatic phase to 0.036 ± 0.021 (Figure 1) and 0.018 ± 0.012 $mg \cdot kg^{-1} \cdot h^{-1}$ (Figure 2) and returned toward the initial values at the postreperfusion phase (0.055 ± 0.018 and 0.032 ± 0.012 $mg \cdot kg^{-1} \cdot h^{-1}$); whereas atracurium requirements remained unchanged during the three phases (0.667 ± 0.199, 0.567 ± 0.142, and 0.692 ± 0.254 $mg \cdot kg^{-1} \cdot h^{-1}$) (Figure 3). No relationship was observed between blood loss and the dose requirement of any of the three drugs throughout the entire procedure.

Discussion

While achieving a constant degree of neuromuscular blockade throughout the three phases of liver transplantation, we observed reduced dose requirements for both vecuronium and pancuronium during the anhepatic phase, whereas the dose requirement of atracurium was unchanged. These results are in agreement with pharmacokinetic data in patients with hepatic disease (1–4).

The evoked integrated electromyographic response of the hypothenar eminence after train-of-four stimulation with the Datex Relaxograph was used in all three groups to allow comparisons to be drawn between the groups. We assume that a steady-state level was reached because the rate of infusion did not vary by more than 20% for each individual patient during each half-hour period for the 2 h preceding the anhepatic phase.

Vecuronium has a shorter duration of action than pancuronium owing to its more rapid clearance from the plasma and its shorter elimination half-life (8). The rapid clearance could be due to redistribution, degradation, or biliary and/or renal elimination. Although the precise action of the liver remains to be determined, all studies are in agreement that the liver is of major importance in the pharmacokinetics and pharmacodynamics of vecuronium (1,2,9–12). The study using vecuronium during OLT in humans showed that plasma clearance was less during the anhepatic phase (13). Our results are in agreement with these findings. The liver is also important in pancuronium metabolism, and altered pharmacokinetics are seen in patients with cirrhosis (3) and total biliary obstruction (14). Our results are also in keeping with these findings. On the other hand, the pharmacokinetics of atracurium have been studied extensively (15–18). Atracurium is hydrolyzed by nonspecific esterases and spontaneously decomposes at physiologic pH and temperature by Hofmann elimination (19). No increase in plasma atracurium levels was found during the anhepatic phase of OLT in pigs (5), showing that the plasma concentration and neuromuscular effect of atracurium was not influenced by the absence of hepatic function or circulation and that the liver does not play a role in its plasma clearance. Another study in anhepatic pigs supports this finding (20) as does the one study during OLT in humans, which failed to show a statistically significant change in atracurium requirement during the three phases of the operation (7).

Many hepatic and nonhepatic factors alter neuromuscular blocker requirements, and several of these may be encountered during the course of OLT. Nonhepatic factors that enhance neuromuscular blockade include acidosis, hypocalcemia, hypokalemia, and hypermagnesemia. When these occurred, appropriate adjustments were made to rectify abnormalities quickly. Acidosis reduces Hofmann elimination as does hypothermia, but it increases ester hydrolysis, which is also involved in the metabolism of atracurium (21). Respiratory acidosis augments twitch tension if it occurs during an infusion of vecuronium (22). The timing of the changes, not the degree of change, has therefore been shown to be of importance. Measures were taken to limit hypothermia, which also prolongs neuromuscular blockade. Blood loss and the volume of blood and fresh frozen plasma replaced in all groups did not show a statistically significant difference.

We conclude that the exclusion of the liver from the circulation accounts for the reduced requirements of vecuronium and pancuronium and that the liver therefore must act as an important organ in the clearance of these two drugs. The requirements of vecuronium and pancuronium when the liver was removed were 50% and 43%, respectively, of the requirements during phase 1. It is not possible from this work to say how the absence of the liver causes this effect; but as steady level conditions existed before removal of the liver, it can be concluded that the altered requirements were due to the absence of metabolism or to the excretion of vecuronium and pancuronium into the bile or both. The size of this reduction in pancuronium requirements is somewhat unexpected. As the kidney is normally the main route of extraction of pancuronium, removal of the liver might be expected to have little effect. However, the metabolic roles of the liver and kidney may be unbalanced in patients with cirrhosis. Thus, this reduction in pancuronium requirements to 43% during the anhepatic phase might be accounted for in part by altered renal function. These results also suggest that the metabolism of atracurium is independent of liver function, as no statistically significant alterations in dose was needed during the period of liver exclusion. This is in keeping with those who have shown the importance of plasma and tissue metabolism (19). In addition, the fact that the dose requirements increased again when the grafted liver was in place suggests that the liver starts functioning after revascularization and removes vecuronium and pancuronium to the same degree as during the dissection phase.

In conclusion, removal of the liver significantly reduces requirements of vecuronium and pancuronium reflecting its role in their elimination, whereas the requirements of atracurium remain unaltered. Thus, an atracurium infusion during OLT provides stable neuromuscular blockade without the need for frequent alterations in the infusion rate.

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Ventilatory Effects of Premedication With Clonidine

Dan Benhamou, MD, Yves Veillette, MD, FRCPC, Patrick Narchi, MD,
and Claude Ecoffey, MD

Département d'Anesthésie-Réanimation, Université Paris-Sud, Hôpital Antoine Béclère, Clamart, France

Clonidine has been proposed as a premedication before surgery because of its beneficial effects on hemodynamics, especially in patients with a high cardiovascular risk. However, reports on the effects of clonidine on ventilation are conflicting. Accordingly, eight fasting ASA physical status I volunteers received in a double-blind randomized order 300 μg of oral clonidine, the effects of which were compared with placebo given in a crossover design. Hypotension, bradycardia, and sedation were significantly more profound and of longer duration after clonidine. Clonidine did not decrease minute ventilation more than the placebo, and separate analysis of tidal volume and respiratory rate changes also showed the absence of a significant difference between the two groups. However, clonidine produced episodes of obstructive pattern associated with moderate decreases in oxygen saturation, which were not observed with placebo. We conclude that the potential detrimental effects of these obstructive airway patterns of clonidine should be taken into account when prescribing this drug for premedication.

(Anesth Analg 1991;73:799–803)

Clonidine, an α_2-adrenergic agonist, has been proposed for premedication to attenuate sympathetic outflow and reduce hemodynamic variability during the perioperative period (1,2). Presumably, preoperative administration of clonidine will decrease hemodynamic variability and facilitate avoiding myocardial ischemia in high-risk patients. Clonidine also has sedative and anxiolytic properties (3). All these properties suggest that clonidine may well be an important component of the premedication in the near future. Because the respiratory effects of clonidine are not clear (4–6), we studied this question in a double-blind, randomized, placebo-controlled, crossover study.

Methods

After institutional approval and informed consent were obtained, eight healthy normotensive volunteers (ASA physical status I, age 31 ± 4 yr, weight 75 ± 7 kg [mean ± SD]) were studied. After an overnight fast, they received in a double-blind randomized order placebo or a pill containing 300 μg of clonidine in 30 mL of water. Tablets containing both placebo and clonidine had been previously prepared and coded by our hospital pharmacy. Studies were performed using a crossover design, at least 1 wk apart, and began at 8 AM. Before drug administration, subjects were allowed to rest supine quietly in a darkened room for 15 min while breathing room air. Arterial blood pressure (systolic, diastolic, and mean) and heart rate were monitored using an automatic cuff pressure device (Dinamap). Sedation was assessed by the same investigator (Y. V.) using a four-point scale where 0 = no sedation, 1 = slight sedation, 2 = drowsy, and 3 = asleep. Breathing pattern was recorded continuously using a respiratory inductive plethysmograph (RIP) (Respitrace) that consisted of two transducer bands worn around the rib cage and abdomen. These two signals were electronically summed to give a third signal corresponding to tidal volume. The three signals were calibrated using a pneumotachograph (Fleisch #2 connected to a differential pressure transducer [Validyne, MP45, ± 2 cm H_2O]) in both the sitting and the supine positions. These signals were continuously recorded and displayed on a paper recorder at a speed of 1 mm/s. This speed, although very slow, was chosen because it permits breathing patterns to be assessed precisely and detects abnormal ventilatory patterns with classifications derived from the study of Frater et al. (7) and defined as follows: central apnea = a period of 15 s or longer without any ventilatory movement, obstructive

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Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Accepted for publication August 13, 1991.

Address correspondance to Dr. Benhamou, Département d'Anesthésie-Réanimation, Université Paris-Sud, Hôpital Antoine Béclère, 157 rue de la Porte de Trivaux, 92141, Clamart, France.

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0003-2999/91/$3.50

apnea = a period of 15 s or longer of obstructed breathing followed by arousal and deep breaths, periodic breathing = a cyclically varying ventilatory signal with gradual increase and decrease in tidal volume. Every 15 min, the paper speed was accelerated to 10 mm/s during 2 min to calculate tidal volume, respiratory rate, and minute ventilation (VE). Analysis of ventilatory patterns was performed by a blinded observer unaware of the drug regimen. Arterial oxygen saturation was continuously recorded using a Nellcor N200 probe attached to the great toe. Hypoxemia was considered moderate when Sa_{O_2} was between 91% and 94% and severe when it was equal to or less than 90%. Arterial blood pressure, heart rate, ventilation, and sedation were assessed every 15 min for 3 h.

Results are expressed as mean ± SD. Statistics included a two-way analysis of variance for repeated measures followed by multiple comparisons within and between groups using a Neuman-Keuls test for analysis of quantitative data and a χ^2 test with Yates' correction for nonparametric data (sedation and abnormal ventilatory events).

Results

Results concerning arterial blood pressure and heart rate are reported in Table 1. Mean arterial blood pressure decreased to 82% of control values after clonidine administration and to 95% of control values after placebo. The difference was statistically significant from 75 to 150 min after clonidine administration. Similar differences could be observed when examining the effects of placebo or clonidine on systolic and diastolic arterial blood pressures (data not shown) and heart rate (Table 1). Sedation was compared between the two groups by calculating the mean percentage of time spent by every patient in each of the four stages of sedation (previously defined), throughout the procedure. Subjects were sedated after having received clonidine and placebo. However, sedation was more profound and of longer duration after clonidine (Figure 1). All respiratory inductive plethysmograph calibration factors were within 10% of the original values. Analysis of ventilatory variables showed significant alterations in both tidal volume, respiratory rate, and minute ventilation (Table 2) when compared with the control period. However, tidal volume, respiratory rate, and minute ventilation were not significantly different at any time when comparing clonidine and placebo. Mean arterial oxygen saturation values measured intermittently every 15 min showed no difference versus control values (Table 2). However, three episodes of moderate decrease in oxygen saturation lasting less than 2 min occurred in three subjects after they had received clonidine and were observed at times of abnormal ventilatory patterns: desaturation was linked to an obstructive pattern in all three cases. Periodic breathing was present in the three patients. In no case was periodic breathing associated with desaturation.

Discussion

Our data confirm the previously demonstrated hemodynamic effects of orally administered clonidine (8–10) and clarify the respiratory efffects of this drug. Sedation was also present in every volunteer and may play a central role in the physiologic alterations observed.

The administration of clonidine produced a larger and longer decrease in arterial blood pressure and heart rate than those observed after placebo administration. These changes remained moderate (3) within the range of that already observed by previous investigators (8–10). Sedation was more profound and longer after clonidine as compared with placebo in every patient. Interestingly, at the time at which hemodynamic changes were maximal, sedation was also maximal. This temporal relationship has already been observed with α_2-agonists (11) and may indicate a physiologic relationship between the sedative and hypotensive actions of clonidine. Profound sedation—as observed after clonidine administration—probably reduces oxygen requirements (12), and hypotension may simply represent an adaptative response to a decrease in oxygen consumption (13). There are, however, arguments against this relationship as the sole explanation. In our crossover study, the hemodynamic effects of sedation and clonidine could be assessed in the same subjects. Yet, the subjects were asleep after placebo, but cardiovascular changes were more pronounced with clonidine. Sedation cannot entirely explain the hemodynamics of clonidine.

The respiratory effects of clonidine are less well known. Although clonidine's pharmacologic effects partially resemble those of opioids, respiratory depression has not been a clinical problem (3). In our study we only observed obstructive respiratory disturbances that occasionally led to transient hypoxemia, whereas decreases in minute ventilation were not significantly different after clonidine than after placebo. Although the literature regarding the ventilatory action of α_2-agonists is not clear, there might be a species- or a dose-related explanation. For instance, dexmedetomidine did not change the slope of the VE-$P_{ET}CO_2$ curve in dogs (14) but markedly increased Pa_{CO_2} in rabbits (15). Human studies also provide conflicting data. In volunteers taking 300–400 μg of oral clonidine, Bailey et al. were unable to document any change in the ventilatory response to inhalation

Table 1. Hemodynamic Effects of 300 μg of Clonidine Given Orally in Healthy Volunteers

	Time												
	Before	15 Min	30 Min	45 Min	60 Min	75 Min	90 Min	105 Min	120 Min	135 Min	150 Min	165 Min	180 Min
MAP (mm Hg)													
Placebo	88 ± 8	85 ± 6	84 ± 10^a	84 ± 6	83 ± 8^a	91 ± 8	85 ± 8	86 ± 4	83 ± 6	86 ± 6	84 ± 7	85 ± 9	85 ± 8
Clonidine	85 ± 8	84 ± 5	78 ± 3^a	80 ± 8^a	80 ± 10^a	80 ± 9^{a,b}	78 ± 6^a	75 ± 8^{a,b}	76 ± 8^a	73 ± 8^{a,b}	70 ± 8^{a,b}	73 ± 7^a	73 ± 8^a
HR (beats/min)													
Placebo	60 ± 7	57 ± 7	55 ± 5^a	55 ± 9^a	55 ± 8^a	57 ± 9	58 ± 10	56 ± 9	55 ± 7^a	57 ± 8	62 ± 10	58 ± 7	57 ± 8
Clonidine	59 ± 6	56 ± 5	51 ± 5^a	52 ± 4^a	53 ± 4^a	56 ± 8	52 ± 6^a	52 ± 6^a	54 ± 12	51 ± 5^a	50 ± 5^{a,b}	51 ± 7	53 ± 8

MAP, mean arterial blood pressure; HR, heart rate.
Values are mean ± SD.
$^a p < 0.05$ vs baseline.
$^b p < 0.05$ clonidine vs placebo.

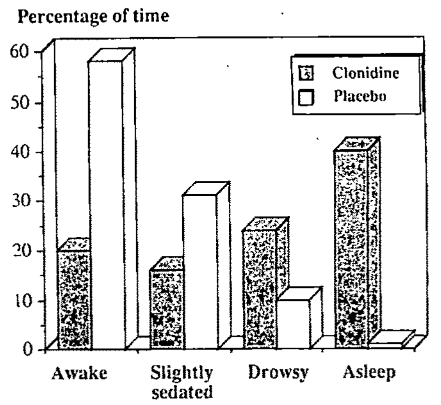

Figure 1. Sedation: results are expressed as the percentage of time spent by patients in each of the four stages of sedation during the study period.

of CO_2 (4), whereas after 300 μg of epidural clonidine and after 300 μg of oral clonidine, Penon et al. (5) and Rougé et al. (6) described a deep sedation and decreases in the slope of VE-PETCO$_2$. These studies also relate sedation and its consequences on ventilation. Sleep-related decreases in oxygen requirements may reduce the needs for ventilation and induce decreases in cardiac output. However, the transient episodes of hypoxemia always occurring at times of an obstructive ventilatory pattern were bothersome. This combination occurs with other depressant drugs (16) and obstruction-related hypoxemia may well be harmful in high-risk patients.

Because of its sedative, analgesic, anxiolytic, and sympatholytic properties, clonidine (or other α_2-agonists) may represent an important addition to premedication. Premedication with clonidine is beneficial in several patient populations (17–19) and particularly in patients with a high cardiovascular risk (1,2,20). However, the hemodynamic effects of clonidine may be harmful rather than beneficial. As already pointed out by Longnecker (21) and Orko et al. (22), the concomitant bradycardia and hypotension may restrict the use of this drug in patients with hypovolemia or coronary artery disease. Wilton et al. (23) showed that in patients experiencing preoperative silent myocardial ischemia and scheduled for coronary artery bypass grafting, there were fewer episodes of ischemia detected during operation than during sleep or in the premedication-induction period. Marjot and Valentine (24) demonstrated a progressive arterial oxygen desaturation and new electrocardiographic changes in 33% of their patients premedicated with lorazepam, morphine, and droperidol before coronary artery bypass grafting. A variable degree of upper airway obstruction was seen in 66% of these patients. In their study as well as in ours, oxygen desaturation was largest during epi-

Table 2. Ventilatory Variables in the Two Groups

	Time												
	Before	15 Min	30 Min	45 Min	60 Min	75 Min	90 Min	105 Min	120 Min	135 Min	150 Min	165 Min	180 Min
VE (L/min)													
Clonidine	8.6 ± 3.5	6.3 ± 2.2[a]	5.5 ± 1.9[a]	6.2 ± 2.6[a]	6.0 ± 2.3[a]	6.0 ± 1.9[a]	6.3 ± 2.5[a]	5.7 ± 2.5[a]	5.3 ± 1.9[a]	5.2 ± 1.8[a]	5.2 ± 1.8[a]	5.7 ± 2.5	6.7 ± 2.6
Placebo	8.9 ± 4.3	7.0 ± 3.3	7.6 ± 2.8	7.3 ± 3.2	7.0 ± 2.1	6.4 ± 1.3	6.5 ± 2.6[a]	6.9 ± 3.0	6.5± 3.0[a]	6.0 ± 0.9	6.4 ± 1.6	7.2 ± 1.8	7.3 ± 2.1
VT (mL)													
Clonidine	505 ± 152	418 ± 100[a]	367 ± 123[a]	391 ± 105[a]	402 ± 129[a]	397 ± 74[a]	393 ± 139	371 ± 129[a]	371 ± 130[a]	362 ± 129[a]	376 ± 127[a]	395 ± 135	405 ± 126
Placebo	556 ± 166	411 ± 106[a]	441 ± 101	466 ± 108	422 ± 84	738 ± 94	409 ± 84[a]	422 ± 118	407 ± 106[a]	365 ± 30[a]	429 ± 106	465 ± 96	456 ± 103
RR (min^{-1})													
Clonidine	17 ± 6	15 ± 4[a]	15 ± 2[a]	16 ± 3	15 ± 3[a]	15 ± 4[a]	16 ± 2	15 ± 3[a]	14 ± 1[a]	14 ± 1[a]	14 ± 1[a]	14 ± 2[a]	16 ± 2
Placebo	16 ± 4	16 ± 3	17 ± 3	16 ± 4	17 ± 3	15 ± 3	15 ± 3	15 ± 3	16 ± 3	17 ± 3	16 ± 3	16 ± 3	16 ± 2
Sao_2 (%)													
Clonidine	97 ± 2	96 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	97 ± 1	98 ± 2
Placebo	97 ± 1	97 ± 1	98 ± 1	97 ± 1	97 ± 1	97 ± 1	98 ± 1	98 ± 1	98 ± 1	97 ± 1	98 ± 1	97 ± 1	98 ± 2

VE, minute ventilation; VT, tidal volume; RR, respiratory rate; Sao_2, arterial oxygen saturation.
Values are mean ± SD.
[a] $P < 0.05$ vs baseline.

sodes of severe airway obstruction. This would suggest that patients receiving clonidine as part of their premedication should also receive oxygen until arrival in the operating room.

In summary, clonidine produced sedation, decreases in heart rate and arterial blood pressure, and obstructive hypoxemia. These potential detrimental effects of clonidine on respiration should be taken into account when prescribing this drug for premedication.

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Ketamine Inhibits Transsarcolemmal Calcium Entry in Guinea Pig Myocardium: Direct Evidence by Single Cell Voltage Clamp

Victor C. Baum, MD, and Mercedes E. Tecson, BS

Departments of Anesthesiology and Pediatrics, UCLA School of Medicine, Los Angeles, California

To clarify the direct effect of ketamine on calcium entry into myocardium, we directly measured transsarcolemmal calcium entry into single enzymatically dissociated guinea pig myocardial cells by means of the whole cell voltage clamp. Cells were studied in the presence of 0, 10^{-5} M, or 10^{-4} M ketamine. Peak baseline calcium current was similar in all three groups (911 ± 92 pA, 954 ± 66 pA, and 962 ± 54 pA, respectively). During exposure to ketamine, peak calcium current was unchanged in the no-ketamine control group (886 ± 74 pA) but decreased in both the 10^{-5} M group (723 ± 38 pA) and the 10^{-4} M group (798 ± 62 pA) ($P < 0.002$ vs no-ketamine cells for both groups). We conclude that ketamine has a direct inhibitory effect on transsarcolemmal calcium influx in guinea pig myocardial cells.

(Anesth Analg 1991;73:804–7)

Ketamine is often used to anesthetize patients with cardiovascular instability because of its cardiovascular stimulation. This salutary effect may have several origins: central nervous system sympathomimetic effects (1), inhibition of neuronal uptake of catecholamines by sympathetic nerve endings (2), direct vasodilation of vascular smooth muscle (3), and myocardial inotropy. The direct inotropic effect of ketamine and the related compound phencyclidine on myocardium has been reported to be both positive (4–8) and negative (9–22).

Using indirect measures, the inotropic effects of ketamine have been related to effects on transsarcolemmal Ca^{2+} entry. Riou et al. using rats and hamsters, in which ketamine is a positive inotrope, suggested that ketamine increased Ca^{2+} influx (6,8), whereas Rusy and his coworkers using rabbits, in which ketamine is a negative inotrope, suggested that ketamine had a major role in inhibiting transsarcolemmal Ca^{2+} entry into myocardial cells (21).

Because of these varied results, the effect of ketamine on electrogenic Ca^{2+} entry was measured directly, utilizing the whole cell configuration of the voltage clamp in single isolated guinea pig cardiac myocytes.

Methods

This study was approved by the UCLA Chancellor's Animal Research Committee.

Peak Ca^{2+} current was measured in single cardiac ventricular myocytes obtained from adult guinea pigs. Current was measured with cells exposed to no ketamine (control, $n = 10$), 10^{-4} M ketamine ($n = 11$), and 10^{-5} M ketamine ($n = 10$).

Cell Isolation

After administration of intraperitoneal heparin (4000 U) and pentobarbital (75 mg), hearts were rapidly excised and placed in cold Ca^{2+} free Tyrode's buffer (in mM: NaCl 136, KCl 5.4, NaH_2PO_4 0.33, $MgCl_2$ 1.0, HEPES 10.0, glucose 10; pH to 7.4 with NaOH). The atria were removed and the aorta cannulated and perfused with Ca^{2+} free Tyrode's buffer. After 4 min the perfusate was changed to enzyme solution consisting of Ca^{2+} free Tyrode's buffer with 667 mg/L of collagenase (Boehringer Mannheim) and 66.7 mg/L of protease (Boehringer Mannheim). The perfusate was changed after 18 min to low-Ca^{2+} buffer (Tyrode's buffer with 0.2 mM $CaCl_2$) to flush out the enzyme solution. The heart was removed from the cannula and placed in a Petri dish with Tyrode's buffer with 0.2 mM

Supported in part by a grant from the UCLA Academic Senate.
Accepted for publication August 16, 1991.

Address correspondence to Dr. Baum, Department of Anesthesiology, BH-556 CHS, UCLA Medical Center, Los Angeles, CA 90024-1778.

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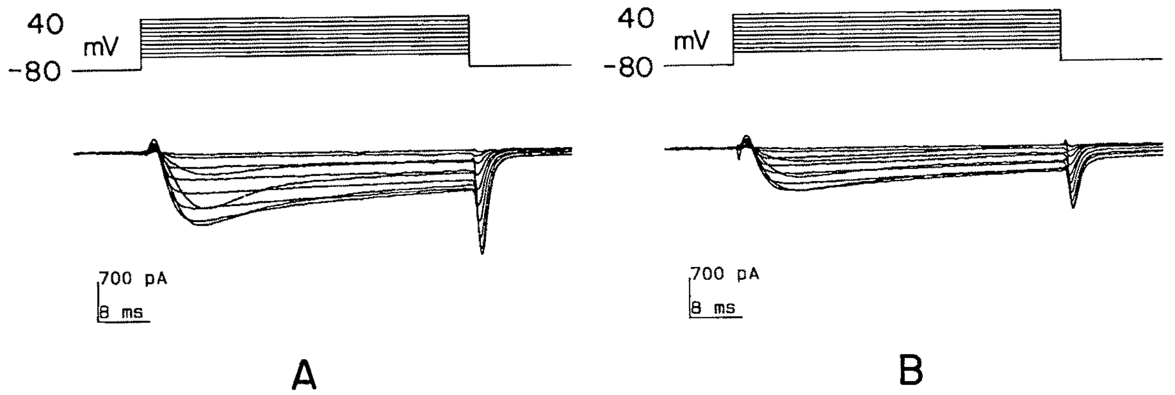

Figure 1. Calcium current recorded from a typical myocardial cell at baseline (**A**) and during exposure to ketamine (**B**). The *top tracing* of each figure represents the steps of the voltage clamp protocol. The currents displayed after return of the clamp to −80 mV represent tail currents.

$CaCl_2$. Individual cells were removed by gentle teasing of the heart and the final concentration of Ca^{2+} in the Petri dish was adjusted to 1.8 mM. All solutions were oxygenated and delivered at 37°C.

Electrophysiologic Recording

A drop of cells was placed in Tyrode's buffer with 1.8 mM $CaCl_2$ in a 0.25-mL chamber mounted on an inverted microscope. Viable cells were easily identifiable by their long thin shape and typical striations. Cells were approached with a glass micropipette filled with a solution containing (in mM) CsCl 145, HEPES 20, EGTA 14, $CaCl_2$ 1, NaCl 10, Mg^{2+}-adenosine triphosphate 5; pH to 7.10 with CsOH. Pipettes were pulled to a tip diameter of approximately 0.5 μm (tip resistance approximately 5 MΩ). The pipettes were mounted on a micromanipulator-mounted headstage of a voltage clamp amplifier (EPC 7, List Electronics, Darmstadt-Eberstadt, Germany). Currents were recorded from voltage-clamped cells by the method of Hamill et al. (23). After the pipette tip contacted a cell, gentle suction created a tight seal between the cell membrane and the glass of the pipette with a resistance in the gigaohm range. The holding potential on the pipette was changed from 0 to −80 mV and additional suction on the pipette caused disruption of the enclosed patch of membrane and established direct continuity with the interior of the cell while maintaining the high resistance seal between the glass wall and the membrane. The cell potential was maintained at −80 mV. Cell potential was regulated by a computer program (pClamp, Axon Instruments, Foster City, Calif.). Net membrane currents were filtered at 2 KHz by an eight-pole Bessel filter (Frequency Devices, Haverhill, Mass.), digitized (Lab Master DMA 1-125, Axon Instruments), and recorded at 50-μs intervals on a hard disk. This system is capable of measuring currents in the 1-pA range.

After establishing the whole cell configuration, the fluid in the chamber was exchanged with three volumes of external solution (in mM: CsCl 145, $MgCl_2$ 1, NaH_2PO_4 0.33, HEPES 10, $CaCl_2$ 1.8, glucose 10, tetrodotoxin 0.01; pH to 7.40 with CsOH) while the cell was clamped at −80 mV. After a 3-min equilibration period, baseline Ca^{2+} currents were evoked by depolarizing cells from −80 mV to potentials between −50 and +40 mV in 10-mV increments for 50 ms. Capacitance artifact and leakage current were electronically subtracted by means of a P/4 routine.

After baseline measurement, the fluid in the chamber was isovolumetrically exchanged with three volumes of external solution containing 0, 10^{-5} M, or 10^{-4} M ketamine (supplied as ketamine HCl powder by Parke Davis). The voltage clamp protocol was repeated after 3 min. The external solution was then exchanged with three volumes of ketamine-free external solution and after 3 min of recovery the clamp protocol was repeated. The use of ketamine-free trials controlled for the phenomenon of Ca^{2+} channel rundown (24) and for any changes due to disturbances caused by the exchange of external fluid.

Statistics

Peak Ca^{2+} currents were compared by analysis of variance and the Newman-Keuls test, with statistical significance considered to be $P < 0.05$. All data are mean ± SEM.

Results

Ca^{2+} currents recorded from a typical cell exposed to ketamine are shown in Figure 1. Baseline peak Ca^{2+} currents were similar in all groups: 911 ± 92 pA in the control group, 954 ± 66 pA in the 10^{-5} M group, and 962 ± 54 pA in the 10^{-4} M group (P = not significant). Peak Ca^{2+} current decreased in 10 of 10 cells exposed

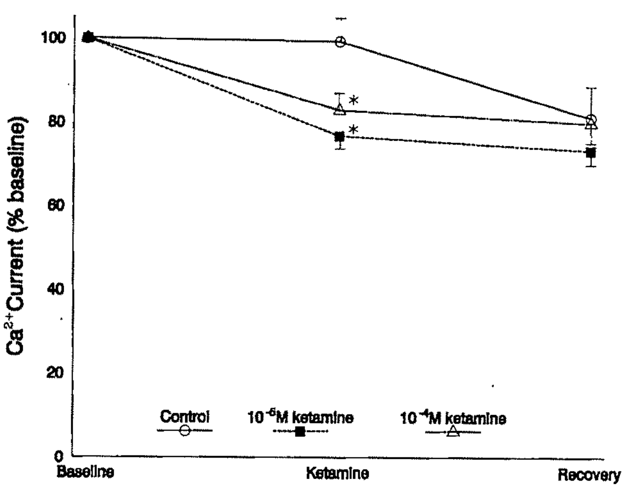

Figure 2. Effect of ketamine exposure on peak Ca^{2+} currents. ○, control cells; ■, 10^{-5} M ketamine; △, 10^{-4} M ketamine. *$P < 0.002$ compared with control cells not exposed to ketamine. Data are mean ± SEM.

to 10^{-5} M ketamine, 10 of 11 cells exposed to 10^{-4} M ketamine, and only 4 of 10 cells in the control group. During exposure to ketamine, peak Ca^{2+} current was unchanged at 886 ± 74 pA in the no-ketamine control group (P = NS vs baseline). In contrast, peak Ca^{2+} current decreased to 723 ± 38 pA in the 10^{-5} M ketamine group ($P < 0.002$ vs control cells) and 798 ± 62 pA in the 10^{-4} M ketamine group ($P < 0.002$ vs control cells). There was no statistical difference between inhibition of Ca^{2+} current caused by 10^{-4} M and 10^{-5} M ketamine. Peak Ca^{2+} current decreased in the control cells by the time of the recovery measurement to a level similar to that in the ketamine-exposed group: 739 ± 104 pA in the control cells, 660 ± 24 pA in the 10^{-5} M cells, and 771 ± 64 pA in the 10^{-4} M cells (P = NS) (Figure 2).

Discussion

The effects of ketamine on myocardium remain unclear. There have been conflicting data reported from a variety of experimental studies. Some of the disparity may be due to species differences. For example ketamine is a positive inotrope in the rat (4,6), ferret (7), and hamster (8), and a negative inotrope in the dog (10,14,15,20), embyronic chick (13), rabbit (9,18,21), and pig (22). However, this cannot be the only source of differences, as ketamine and the related compound phencyclidine are both a positive and negative inotrope in different studies in the rat (4,6,11,19) and the guinea pig (12,16,25). These studies have been done both in vivo and in vitro and have evaluated whole heart, atria, and ventricular papillary muscle or trabeculae. Studies have also differed in the dose range of ketamine evaluated. Some studies have used excessively high doses (10). Several authors have shown that high concentrations (>5 × 10^{-4} M) have a negative inotropic effect (9–11,15,16). Some authors have also shown a temporal factor, with early positive inotropy followed by negative inotropy (19). In addition, several authors, particularly earlier ones, did not control for secondary effects of changes in contraction rate on measured indices of contractility. Levels of extracellular Ca^{2+} in in vitro studies may also have an effect. It may be difficult to document a positive inotropic effect at high levels of extracellular Ca^{2+} at which contractility is already maximal (6).

One of the mechanisms implicated in the action of ketamine is an effect on intracellular Ca^{2+}. Rusy et al. (21), using rabbit papillary muscle, a species in which ketamine is a negative inotrope, evaluated the effects of ketamine on Ca^{2+} entry via the sarcolemma and on Ca^{2+} release from sarcoplasmic reticulum stores. Using ketamine concentrations of 8.4 × 10^{-5} M and 1.7 × 10^{-4} M, they determined that inhibition of transsarcolemmal Ca^{2+} influx is a predominant mechanism in the negative inotropic effect of ketamine. Ketamine had only a small or no effect on indicators of sarcoplasmic reticulum Ca^{2+} release. Riou et al. (6) using rat myocardium, a system in which ketamine is a positive inotrope, concluded that 10^{-4} M and 10^{-5} M ketamine had a positive inotropic effect, probably due to an increase in transsarcolemmal Ca^{2+} influx. However, impaired sarcoplasmic reticulum function at the higher concentration might overcome the positive inotropic effect. They recently confirmed these findings in healthy hamsters, although the positive inotropic effects of ketamine were minimal in cardiomyopathic hamsters (8).

These studies used, as an indicator of Ca^{2+} entry into cells, indirect measures based on the response of papillary muscle to varying loading conditions (6) or stimulating protocols (6,21). Barrigon et al., using rat atria, also suggested that ketamine increased Ca^{2+} influx into myocardium. Their conclusion was based on the abolishment of positive inotropy by verapamil, changes in action potential morphology consistent with increased intracellular Ca^{2+}, and increased ^{45}Ca uptake at ketamine concentrations of < 5 × 10^{-4} M (4).

Because of these varied results using indirect indicators of transsarcolemmal Ca^{2+} entry, we directly measured electrogenic transsarcolemmal Ca^{2+} entry by voltage clamping single whole ventricular myocytes. This method has several advantages. The use of single cells avoids any confounding interactions from vascular effects or effects of ketamine on local or distant catecholamine release. In this system Ca^{2+} release from, or uptake by, sarcoplasmic reticulum is not a confounding variable as intracellular Ca^{2+} is rapidly chelated. Thus the measured current represents transsarcolemmal Ca^{2+} entry. Other ionic currents, specifically the inward Na^+ and outward K^+

currents, were blocked by tetrodotoxin and cesium, respectively. The resultant current represents inward Ca^{2+} current as confirmed by its direction, time-course, and typical current-voltage relationship. Because the specific voltage clamp protocol used does not inactivate the short-lived T-type Ca^{2+} current, the currents measured represented both T- and L-type currents (26).

The inhaled anesthetics also inhibit transsarcolemmal Ca^{2+} entry into myocardial cells (27–29). The decrease in Ca^{2+} entry that we documented by ketamine is similar to the decrease induced by 0.4%–0.7% halothane, 0.4%–0.8% enflurane, and 0.3%–0.6% isoflurane in a recent study of voltage-clamped canine myocardial cells (29).

The concentrations of ketamine that were selected represent approximate blood levels obtained after induction (10^{-4} M) and maintenance (10^{-5} M) of anesthesia (30). At both of these concentrations there was a significant decrease in electrogenic Ca^{2+} entry into ketamine-exposed cells compared with control cells. After recovery from ketamine, there was no significant difference between cells exposed to ketamine and control cells. As noted above, this current represents Ca^{2+} entry into the cell via the sarcolemma and does not measure Ca^{2+} release by the sarcoplasmic reticulum. Thus this study does not address the effect of ketamine on sarcoplasmic reticulum function.

In summary, by means of the isolated whole cell voltage clamp, an inhibitory effect of ketamine on transsarcolemmal Ca^{2+} entry was documented in adult guinea pig ventricular myocytes. Any positive inotropic effect of ketamine in the guinea pig does not involve a directly mediated increase in transsarcolemmal Ca^{2+} entry. This does not exclude a secondary effect on Ca^{2+} entry mediated by catecholamines, other mediators of cyclic adenosine monophosphate levels, or additional mechanisms.

We are grateful to the laboratory of Dr. J. Weiss for making available their expertise in cell isolation. We thank Drs. T. Hales and G. Wetzel for helpful discussions.

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Can Changes in End-Tidal Pco_2 Measure Changes in Cardiac Output?

Schlomo A. Isserles, MD, and Peter H. Breen, MD, FRCPC

Department of Anesthesia and Critical Care, University of Chicago, Chicago, Illinois

In recent studies of cardiopulmonary resuscitation, an increase in end-tidal carbon dioxide tension (P_{ETCO_2}) signifies an increase in cardiac output ($\dot{Q}_T$) as spontaneous circulation resumes. We hypothesized that changes in $\dot{Q}_T$ might generally be measured by changes in P_{ETCO_2}. In five pentobarbital-anesthetized dogs, we inflated percutaneously inserted vena cava balloons to impede venous return and to decrease $\dot{Q}_T$ (measured by pulmonary thermodilution). The P_{ETCO_2} was measured at the airway opening by sidestream infrared capnometry. In 32 vena cava balloon inflation sequences during constant ventilation in five dogs, the percent decrease in P_{ETCO_2} directly correlated with the percent decrease in $\dot{Q}_T$ (slope = 0.73, R^2 = 0.89, $P < 0.001$). During decreased $\dot{Q}_T$, reduced CO_2 delivery to the lungs decreased alveolar Pco_2 to cause part of the decrease in P_{ETCO_2}. The remaining reduction in P_{ETCO_2} resulted from the increase in alveolar dead space (in turn due to lower pulmonary perfusion pressures during reduced $\dot{Q}_T$), which diluted the CO_2 from perfused alveolar spaces to further reduce P_{ETCO_2}. During a sustained reduction in $\dot{Q}_T$, increasing CO_2 accumulation in the peripheral tissues and in venous blood began to restore CO_2 delivery to the lung and P_{ETCO_2} toward baseline levels. Reciprocal changes occurred during increases in $\dot{Q}_T$ when the vena cava balloons were deflated. The linear relationship between changes in P_{ETCO_2} and $\dot{Q}_T$ in animals supports a decision to perform clinical studies necessary to determine whether a change in P_{ETCO_2} will be useful as a noninvasive, continuous monitor of a change in $\dot{Q}_T$ during anesthesia or intensive care.

(Anesth Analg 1991;73:808–14)

The study of the elimination of CO_2 produced by the peripheral tissues has been largely confined to the steady-state condition. During such gas exchange equilibrium, the alveolar Pco_2 (P_{ACO_2}), the tissue CO_2 production ($\dot{V}co_{2[ti]}$), and the alveolar ventilation ($\dot{V}_A$) are uniquely related as given by $P_{ACO_2} \propto \dot{V}co_{2[ti]}/\dot{V}_A$ (1,2). By design, this steady-state approach has ignored the temporal changes in P_{ACO_2} in response to acute perturbations of cardiac output ($\dot{Q}_T$).

A qualitative relationship between $\dot{Q}_T$ and exhaled CO_2 has been demonstrated in various clinical settings. Catastrophic cardiovascular events during anesthesia (e.g., severe hypovolemia, cardiac arrest) cause an exponential decrease in end-tidal Pco_2 (P_{ETCO_2}) within a dozen breaths (3). Recent reports (4–6) imply that changes in P_{ETCO_2} can reflect changes in $\dot{Q}_T$ during cardiopulmonary resuscitation.

We synthesized these observations into the following hypothesis. During constant minute ventilation and $\dot{V}co_{2[ti]}$, an abrupt reduction in $\dot{Q}_T$ reduces P_{ETCO_2} by two mechanisms. First, a reduction in venous return causes a decrease in CO_2 delivered to the alveolar compartment (7), resulting in decreased P_{ACO_2}. Second, the increase in alveolar dead space, in turn resulting from the reduced pulmonary vascular pressures (8–10), will dilute the CO_2 from normally perfused alveolar spaces to decrease P_{ETCO_2} below P_{ACO_2} (10–12). In this study, we test whether acute changes in $\dot{Q}_T$ result in measurable and predictable changes in P_{ETCO_2} during constant $\dot{V}co_{2[ti]}$ and minute ventilation. We inflated balloons in both vena cavae of dogs to impede venous return and which in turn cause a decrease in $\dot{Q}_T$. The resulting change in P_{ETCO_2} was measured. To seek the mechanism underlying this change in P_{ETCO_2}, we also measured temporal changes in the arterial Pco_2 ($Paco_2$, assumed equal to P_{ACO_2}) (2), calculated the alveolar dead space-to-tidal volume ratio (V_D/V_T) (12), and measured the CO_2 volume exhaled by the lung ($\dot{V}co_{2[lung]}$) by collecting expired gas.

Supported by the National Heart, Lung, and Blood Institute (grant HL-42637) and by the ASA Foundation for Anesthesia Education and Research.

Accepted for publication July 26, 1991.

Address correspondence to Dr. Breen, Department of Anesthesia and Critical Care, Box 428, The University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637.

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0003-2999/91/$3.50

Methods

This study was approved by the Animal Research Committee at the University of Chicago Hospitals, in accordance with guidelines accepted by the American Physiologic Society. Five mongrel dogs (body weight, 21.8 ± 2.1 kg) were anesthetized with intravenous pentobarbital (30 mg/kg). After insertion of an orotracheal tube, we began mechanical ventilation (model 613, Harvard Apparatus, South Natick, Mass.) with air, with the dog in supine position. Tidal volume (18.1 ± 1.8 mL/kg) and respiratory frequency (12.0 ± 1.0 min^{-1}) were adjusted to maintain baseline Pa_{CO_2} near 40 mm Hg; during each experimental change in $\dot{Q}_T$, these inspired ventilation values were held constant. The Y-adapter, joining the inspired and expired limbs of the circuit, was connected close to the orotracheal tube to minimize circuit dead space. Exhaled gas exited sequentially through a pneumotachometer (Fleisch No. 2, Menatoba Co., Menatoba, Switzerland), the Harvard ventilator valve bank, and a large-bore three-way stopcock, to intermittently collect exhaled gas in a 5-L bag. Airway opening pressure (P_{ao}) was sensed at the proximal end of the orotracheal tube.

Gas was sampled from the proximal end of the orotracheal tube by an infrared CO_2 analyzer (Gambro Engstrom Eliza, Bromma, Sweden). This capnometer was calibrated before each experiment with a 5% CO_2 mixture. The $\dot{V}_{CO_2}$ eliminated from the lung ($\dot{V}_{CO_2[lung]}$) was determined by collecting expired gas over four to eight breaths. The $\dot{V}_{CO_2[lung]}$ was determined from the calculation of $F_{E_{CO_2}} \cdot V_E \cdot f/n$ breaths, where $F_{E_{CO_2}}$ is the fraction of CO_2 in the mixed expired gas collection, V_E is the collected expired volume determined by integrating $\dot{V}_E \cdot dt$ over n collected breaths (Integrator Amplifier model 13-4615-70, Gould Inc., Cleveland, Ohio), and f is the respiratory frequency.

We cannulated a femoral vein for fluid and drug administration and a femoral artery to measure systemic arterial pressure (P_{sa}) and sample blood for analysis of Pa_{O_2}, Pa_{CO_2}, and pHa. Through the right external jugular vein, we floated a flow-directed pulmonary artery catheter (American Edwards, Irvine, Calif.) into a pulmonary artery branch to monitor pressure (P_{pa}), to intermittently measure pulmonary wedge pressure (P_{pw}), and to measure thermodilution cardiac output ($\dot{Q}_T$). The thermal signal was processed by computer (American Edwards 9520) to determine pulmonary $\dot{Q}_T$.

We assured the accuracy of this thermodilution determination of $\dot{Q}_T$ in several ways (13). In the dog, the proximal port of an adult flow-directed pulmonary artery catheter can lie in the superior vena cava. To avoid transit delay when the Fogarty balloon was inflated in the superior vena cava, the saline indicator (0°C, 5 mL) was injected into the right atrium through a separate catheter. We monitored the thermistor temperature to ensure a stable baseline, an appropriate signal-to-noise ratio (improved by larger, colder saline injections), and a smooth contoured curve (rapid upstroke followed by an exponential decay). Determinations of $\dot{Q}_T$ in duplicate (50 s each) were preceded by a dummy saline injection to minimize aberrant temperature changes in the injectate. The $\dot{Q}_T$ measurements began at the same phase in ventilation to minimize respiratory-cardiovascular interactions (14).

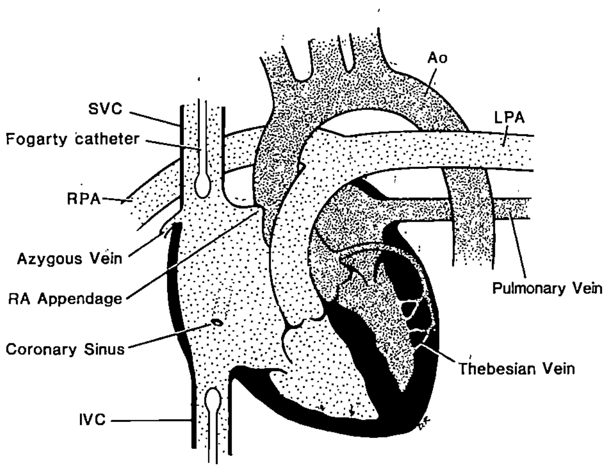

Figure 1. Fogarty catheter balloon position in the proximal superior and inferior vena cava (SVC and IVC) to control venous return and cardiac output. LPA and RPA, left and right pulmonary arteries; Ao, aorta.

The P_{ao} was monitored using a differential pressure transducer (Validyne DP45-28, Northridge, Calif.) that was excited and conditioned by a Validyne CD-19 carrier demodulator. Vascular pressures were measured with Gould transducers (model P23, Oxnard, Calif.). All signals were amplified and recorded on a eight-channel polygraph (Gould 2800S, Cleveland, Ohio).

Through the external jugular and femoral veins, we advanced two Fogarty catheters (10F, 4-mL balloon capacity, American Edwards, Irvine, Calif.) into the right atrium using external estimations of distance (Figure 1). After balloon inflation, the catheters were slowly withdrawn. The onset of resistance to catheter withdrawal signaled balloon position at the right atrium orifices of the vena cavae. Then, the balloon was deflated and the catheter was further withdrawn 2–3 cm to position the catheter tip in the proximal superior or inferior vena cava. Inflation of these balloons impeded venous return to the right atrium causing a reduction in $\dot{Q}_T$. Animals were paralyzed with intravenous pancuronium bromide (0.2 mg/kg). During the experiment, maintenance doses of pentobarbital (2.4 ± 0.5 mg/kg) and pancuronium bromide (0.09 ± 0.01 mg/kg) were administered hourly.

For each experimental sequence, we conducted baseline measurements: arterial blood sample for gas tensions and pH, P_{sa}, P_{pa}, PETCO$_2$, $\dot{V}CO_{2[lung]}$, and $\dot{Q}$T. Then, we inflated the vena cava balloons and repeated measurements after peak reduction of PETCO$_2$ (about 10 breaths). The balloons were then deflated to increase $\dot{Q}$T back toward baseline, and measurements were conducted when PETCO$_2$ again reached its peak. We conducted 32 of these vena cava balloon inflation sequences in five dogs, using variable balloon volumes to generate a wide range of $\dot{Q}$T changes.

In each dog, we then measured these same variables during a sustained decrease in $\dot{Q}$T. After completing measurements before and after the initial inflation of the vena cava balloons (see preceding paragraph), we maintained inflation of the vena cava balloons and conducted measurements for up to 45 min (see abscissa of Figure 6 for measurement intervals).

Blood gases and pH were measured with a Radiometer ABL-2 (Copenhagen, Denmark) at 37°C and then corrected to body temperature (15). The Engstrom Eliza capnometer sampling tube is permeable to H_2O vapor (but not other gases). The resulting dry measurement of P_{CO_2} is converted to a saturated value by multiplying it by the factor $(P_B - P_{H_2O})/P_B$, where P_B is the total barometric pressure and P_{H_2O} is the water vapor pressure at body temperature.

The alveolar dead space-to-tidal volume ratio (VD/VT) is the fraction of alveolar volume that does not receive pulmonary perfusion. The calculation of alveolar VD/VT (12) is portrayed in the two-compartment lung model shown in Figure 2. A linear dissociation curve of CO_2 content as a function of P_{CO_2} in blood is assumed (16), and rebreathing from perfused alveolar space into alveolar dead space is ignored. Then, we may write

$$(\text{Alveolar VT} - \text{Alveolar VD})\cdot \text{PACO}_2/\text{PB} = \text{Alveolar VT}\cdot\text{PETCO}_2/\text{PB}$$

or

$$\text{Alveolar VD/VT} = (\text{PACO}_2 - \text{PETCO}_2)/\text{PACO}_2.$$

Assuming $\text{Paco}_2 = \text{PACO}_2$ (2), then alveolar VD/VT = $(\text{Paco}_2 - \text{PETCO}_2)/\text{Paco}_2$. For example, the variable values shown in Figure 2 generate an alveolar VD/VT = (40 − 20)/40 = 0.5.

Data are reported as mean ± 1 SD. Correlation between variables was determined using a multiple linear regression model (17) that had a common slope and separate intercepts for each dog. The slope, R^2 (coefficient of determination), and P value are reported for each linear regression.

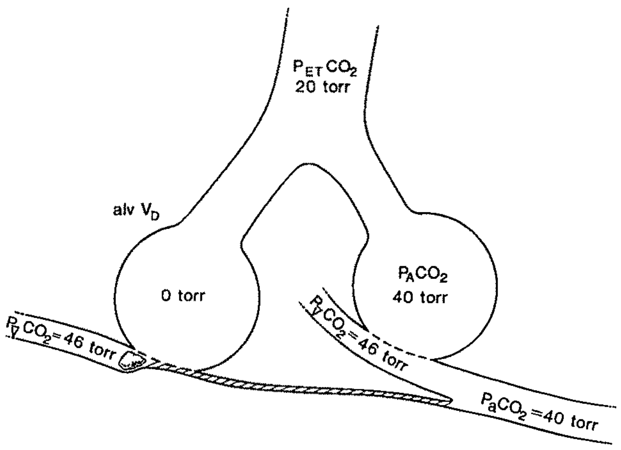

Figure 2. Two-compartment lung model consisting of an alveolar dead space unit (alv VD) and a normally perfused and ventilated unit. The ratio of alv VD to alveolar tidal volume (VT) may be written as alveolar VD/VT = (PACO$_2$ − PETCO$_2$)/PACO$_2$ (Reference 12), where PETCO$_2$, PACO$_2$, Paco$_2$, and Pvco$_2$ are the end-tidal, alveolar, arterial, and mixed venous P_{CO_2}, respectively. See text for details. (Modified from Reference 3.)

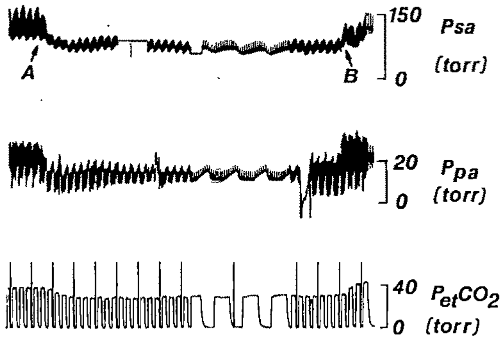

Figure 3. Effect of vena cava balloon inflation (*point A*) and deflation (*point B*) on variables in dog 2. Cardiac output decreased from 2.8 to 1.5 L/min during balloon inflation. P_{sa}, systemic arterial blood pressure; P_{pa}, pulmonary artery pressure; PETCO$_2$, end-tidal P_{CO_2}.

Results

A polygraph recording of a representative inflation/deflation sequence of the vena cava balloons in dog 2 (Figure 3) shows the usual changes that we observed. Point A marks inflation of the superior vena cava and inferior vena cava balloons. When $\dot{Q}$T decreased from 2.8 to 1.5 L/min, there were parallel decreases in PETCO$_2$ (38 to 28 torr) and $\dot{V}CO_{2[lung]}$ (155 to 108 mL/min). After deflation of the vena cava balloons (point B) to increase $\dot{Q}$T, PETCO$_2$ and $\dot{V}CO_{2[lung]}$ returned toward baseline.

Acute Effects of Vena Cava Balloon Inflation

In 32 vena cava balloon inflation sequences in five dogs, there was a significant linear correlation be-

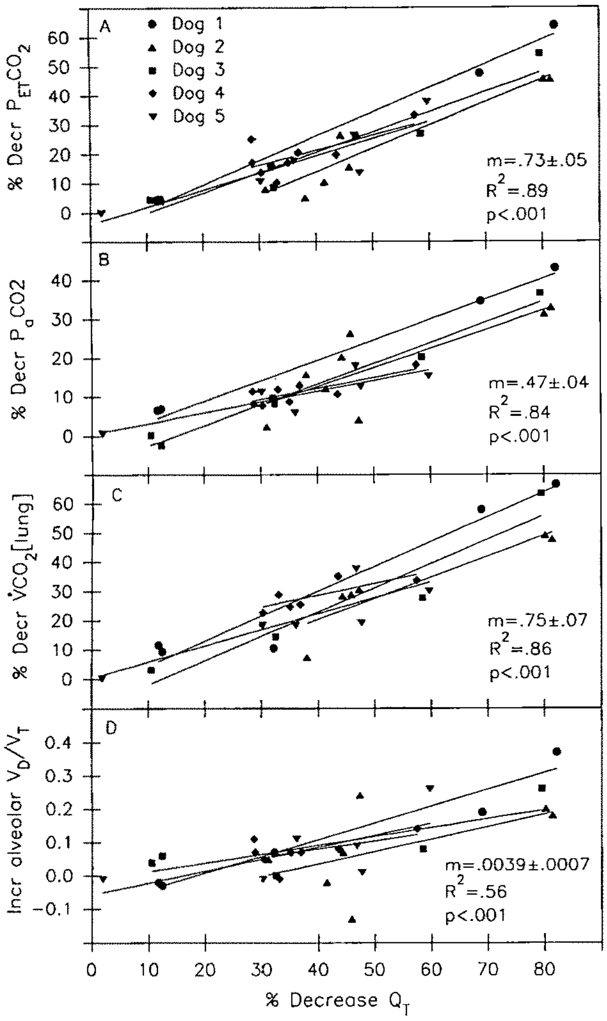

Figure 4. Effects of 32 vena cava balloon inflation sequences in five dogs to decrease cardiac output ($\dot{Q}$T). During each balloon inflation sequence, the y-axis variable is correlated against the percent decrease in $\dot{Q}$T. *Panel A* is the percent decrease in end-tidal Pco$_2$ (PETCO$_2$); *panel B* is the percent decrease in arterial Pco$_2$ (Paco$_2$); *panel C* is the percent decrease in $\dot{V}$co$_2$ eliminated from the lung ($\dot{V}$co$_{2[\text{lung}]}$); and *panel D* is the arithmetic increase in alveolar dead space/tidal volume ratio (VD/VT). The linear regression line for each dog is shown. m, Average (± SD) slope for five dogs; R^2, coefficient of determination.

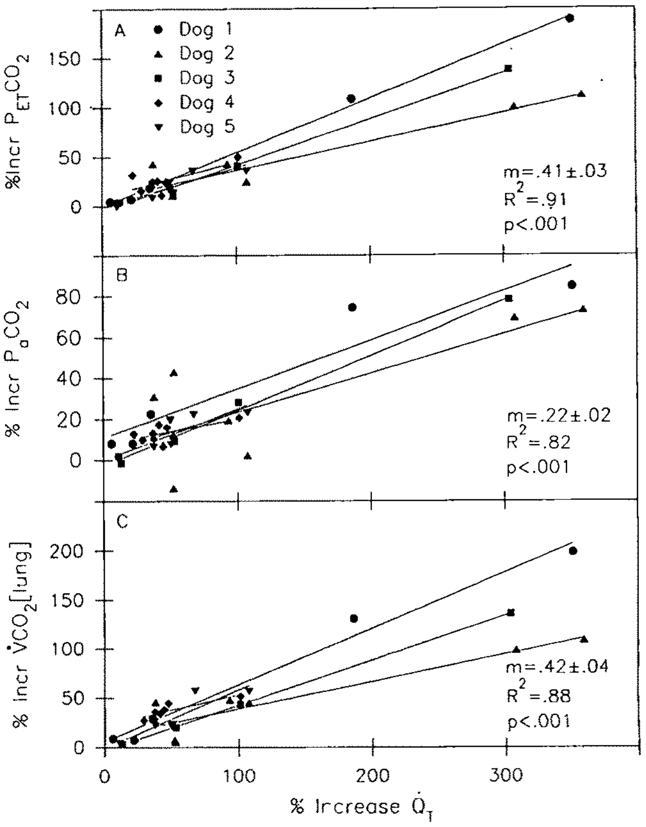

Figure 5. Effects of 32 vena cava balloon deflation sequences in five dogs to increase cardiac output ($\dot{Q}$T). During each balloon deflation sequence, the y-axis variable is plotted against the percent increase in $\dot{Q}$T. *Panel A* is the percent increase in end-tidal Pco$_2$ (PETCO$_2$); *panel B* is the percent increase in arterial Pco$_2$ (Paco$_2$); and *panel C* is the percent increase in $\dot{V}$co$_2$ eliminated from the lung ($\dot{V}$co$_{2[\text{lung}]}$). The linear regression line for each dog is shown. m, Average (± SD) slope for five dogs; R^2, coefficient of determination.

tween the percent decreases in PETCO$_2$ and $\dot{Q}$T (Figure 4A, slope = 0.73). A similar slope (0.75) existed between the percent decreases in $\dot{V}$co$_{2[\text{lung}]}$ and $\dot{Q}$T (Figure 4C).

The percent decrease in Paco$_2$ (which estimated PAco$_2$) also linearly correlated with the percent decrease in $\dot{Q}$T (Figure 4B). During a $\dot{Q}$T decrease, the decrease in Paco$_2$ (slope = 0.47) accounted for 64% (0.47/0.73) of the decrease in PETCO$_2$ (slope = 0.73). The resulting increase in the Paco$_2$–PETCO$_2$ gradient, normalized for the starting Paco$_2$, represented the increase in alveolar VD/VT when $\dot{Q}$T decreased (Figure 4D). This increase in alveolar VD/VT during decreases in $\dot{Q}$T in turn linearly correlated with the reduction in P_{pa} that occurred (slope = 0.0032 ± 0.0008, R^2 = 0.379, $P < 0.001$).

Acute Effects of Vena Cava Balloon Deflation

When the vena cava balloons were deflated to increase $\dot{Q}$T, opposite changes in variables occurred (compared with the balloon inflation sequence). In fact, these CO$_2$ variables all overshot their baseline values, as the increased peripheral tissue stores of CO$_2$ rushed back to the lung (18). Note that during a sequence of $\dot{Q}$T increase, measurements necessarily began after the transient non-steady-state period of reduced $\dot{Q}$T during vena cava balloon inflation.

During the increases in $\dot{Q}$T, there were significant linear percent increases in PETCO$_2$ (Figure 5A), Paco$_2$ (Figure 5B), and $\dot{V}$co$_{2[\text{lung}]}$ (Figure 5C). The Paco$_2$–PETCO$_2$ gradient or alveolar VD/VT significantly decreased when $\dot{Q}$T increased; this decrease in alveolar

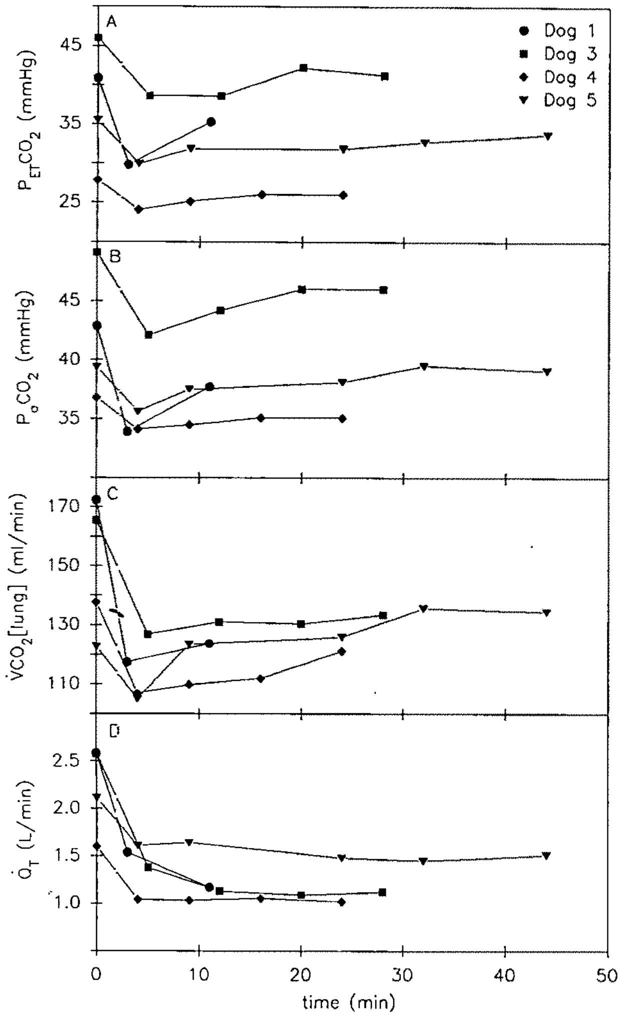

Figure 6. Effects of sustained reduction in cardiac output ($\dot{Q}$T) in four dogs. PETCO$_2$, end-tidal Pco$_2$; Paco$_2$ arterial Pco$_2$; $\dot{V}$co$_{2[lung]}$, $\dot{V}$co$_2$ eliminated from the lung.

VD/VT in turn correlated ($P < 0.001$) with the increase in P_{pa} that occurred when $\dot{Q}$T increased.

Effects of Sustained Vena Cava Balloon Inflation

Maintenance of a stable decreased $\dot{Q}$T by sustained inflation of the vena cava balloons was difficult because a balloon volume change as small as ⅓ mL could result in large changes in $\dot{Q}$T. However, in four dogs, we were able to maintain a relatively stable, decreased $\dot{Q}$T for periods up to 45 min at a constant tidal volume (Figure 6D). After an initial decrease in PETCO$_2$ (similar to the acute decreases in PETCO$_2$ shown in Figure 4A), PETCO$_2$ tended to increase back toward baseline during continued low $\dot{Q}$T (Figure 6A). These changes in PETCO$_2$ were paralleled by the changes in Paco$_2$ and $\dot{V}$co$_{2[lung]}$ (Figures 6B and 6C, respectively).

Discussion

During equilibrium, PAco$_2$ depends only on the tissue CO$_2$ production ($\dot{V}$co$_{2[ti]}$) and alveolar ventilation ($\dot{V}$A) (PAco$_2$ $\propto$ $\dot{V}$co$_{2[ti]}$/$\dot{V}$A) (1,2). During steady state, the value of cardiac output ($\dot{Q}$T) will not affect PAco$_2$ (to the extent that the alveolar dead space-to-tidal volume ratio [VD/VT] does not change). Only during non-steady state can changes in pulmonary perfusion affect PAco$_2$ (7,19). We believe that attention in both the clinical and physiological arenas has been focused on mechanisms during steady state; the transient non-steady-state condition, although first addressed 30 yr ago (20,21), has been mostly avoided in more recent work. Now, interest in the transient effects of $\dot{Q}$T changes on CO$_2$ stores has been rekindled with the observations of exhaled CO$_2$ as an indicator of effective $\dot{Q}$T during cardiopulmonary resuscitation (4,22).

The correlation of changes in $\dot{Q}$T and end-tidal Pco$_2$ (PETCO$_2$) was first observed a few years after the introduction of measured exhaled CO$_2$ as an on-line monitor of pulmonary ventilation (23). Leigh et al. (20) demonstrated that alveolar CO$_2$ concentration decreased when pulmonary blood flow decreased in a variety of conditions during cardiothoracic surgery including systemic hypotension, acute heart failure, occluded systemic circulation, and ineffective cardiac massage during cardiopulmonary resuscitation. In 1961, Leigh et al. (21) further emphasized the ability of capnography to also detect a reduction in $\dot{V}$co$_{2[ti]}$ owing to hypothermia and demonstrated that CO$_2$ storage occurs in body regions to which perfusion is occluded. That changes in exhaled CO$_2$ concentration are linked to interrelated effects of $\dot{V}$co$_{2[ti]}$, pulmonary perfusion, and ventilation have been confirmed in more recent reports (3,24,25). In the last few years, studies of cardiopulmonary resuscitation both in animal models (6,22) and in patients (4,5,26) have demonstrated a correlation between PETCO$_2$ and effective $\dot{Q}$T.

In this study, we have demonstrated that an acute decrease in PETCO$_2$ can predictably reflect an acute decrease in $\dot{Q}$T in dogs when fixed ventilation is maintained and constant $\dot{V}$co$_{2[ti]}$ is assumed. What is the mechanism by which an acute $\dot{Q}$T decrease causes a decrease in PETCO$_2$? One factor may be the decreased delivery of CO$_2$ to the lung and another, the increase in alveolar spaces with high ventilation-to-perfusion ratios ($\dot{V}$A/$\dot{Q}$) or even an increase in alveolar VD/VT (12). The alveolar VD/VT is the fraction of ventilated but nonperfused lung units, i.e., West's zone I of the lung (27). By rearranging the formula for alveolar VD/VT (see Methods and Figure 2), PETCO$_2$ is given by PAco$_2$·(1 − alveolar VD/VT). Thus, during a decrease in $\dot{Q}$T, a decrease in PETCO$_2$ may result from a decrease in $P\text{ACO}_2$ and/or an increase in alveolar V_D/V_T.

During the reduction in $\dot{Q}_T$, $P\text{aCO}_2$ (or $P\text{ACO}_2$) decreased to account for 64% of the decrease in $P\text{ETCO}_2$. The $P\text{ACO}_2$ decreased because the reduction in $\dot{Q}_T$ decreased CO_2 delivery to the lung while fixed ventilation continued to eliminate CO_2 from the lung. Constant tissue $\dot{V}\text{CO}_2$ is assumed. At the same time, alveolar V_D/V_T increased as $\dot{Q}_T$ decreased (Figure 4D). During expiration, this increased alveolar V_D diluted the CO_2 exhaled from perfused alveolar spaces to decrease the $P\text{ETCO}_2$ below the $P\text{ACO}_2$ (12). During a reduction in $\dot{Q}_T$, alveolar V_D/V_T increased because the reduction in pulmonary perfusion pressures (8–10) converted lung regions to function as though they were West zone I.

The $\dot{V}\text{CO}_{2[\text{lung}]}$ decreased as $\dot{Q}_T$ decreased (Figure 4C). This reduction in CO_2 eliminated from the lung reflects the decreased CO_2 delivery to the lung. Analogous to the effects of $\dot{Q}_T$ on $P\text{ETCO}_2$, $\dot{V}\text{CO}_{2[\text{lung}]}$ also decreased because the increase in alveolar V_D/V_T decreased the effective alveolar ventilation.

Four factors may counter the decrease in $P\text{ETCO}_2$ that occurs during a decrease in $\dot{Q}_T$. First, the increase in alveolar V_D/V_T will decrease effective alveolar ventilation ($\dot{V}_A$) (11), reduce CO_2 elimination from the lung, and tend to increase the $P\text{ACO}_2$. Second, the decrease in mixed venous oxygen saturation of hemoglobin that occurs during a decrease in $\dot{Q}_T$ (28) will increase the capacity of the mixed venous blood to carry CO_2 at a given $P\text{CO}_2$ (Haldane effect [29]) that will also offset the decrease in CO_2 delivery when $\dot{Q}_T$ decreases. Third, the alveolar tissue CO_2 stores themselves will buffer (by a small amount) the fall in $P\text{ACO}_2$ (0.38 mL of CO_2 STPD·[100 mL lung tissue]$^{-1}$·mm Hg^{-1}) (30). Fourth, during sustained decrease in $\dot{Q}_T$ (Figure 6), $P\text{ETCO}_2$ and $P\text{aCO}_2$ initially decreased, similar to the results shown in Figure 4. During continued decrease in $\dot{Q}_T$, CO_2 transport to the lungs was reduced and CO_2 began to accumulate in the periphery. Thus, the CO_2 content (and $P\text{CO}_2$) in the peripheral tissues and the returning venous blood increased and began to restore CO_2 delivery to the lung (16,19). Consequently, during continued decreased $\dot{Q}_T$, the $P\text{ETCO}_2$, $P\text{aCO}_2$, and $\dot{V}\text{CO}_{2[\text{lung}]}$ tended to increase back toward baseline (Figure 6).

A similar phenomenon has been noted during cardiopulmonary resuscitation in patients (18). During decreased $\dot{Q}_T$ during cardiac arrest, the peripheral venous $P\text{CO}_2$ increased. This increase in peripheral venous $P\text{CO}_2$ reflected the accumulation of CO_2 in the peripheral tissue compartment during low $\dot{Q}_T$. All these mechanisms that underlie CO_2 transport assume a constant $\dot{V}\text{CO}_{2[\text{ti}]}$. However, $\dot{Q}_T$ could decrease below a level that supports critical oxygen delivery to the tissues (31). Then, tissue metabolism and CO_2 production would decrease below baseline levels. This potential reduction in $\dot{V}\text{CO}_{2[\text{ti}]}$ during sustained low $\dot{Q}_T$ would then contribute to decreases in $P\text{ETCO}_2$ and $P\text{aCO}_2$.

We chose to present data as percent change in $P\text{ETCO}_2$ versus percent change in $\dot{Q}_T$, rather than comparing arithmetic changes in these variables. We reasoned that at a lower starting $\dot{Q}_T$, a given $\dot{Q}_T$ decrease should cause a larger decrease in $P\text{ETCO}_2$, because a larger fractional reduction in CO_2 delivery to the lungs would occur. Two alternate data presentations support this contention. First, the plot of arithmetic decreases in $P\text{ETCO}_2$ versus $\dot{Q}_T$ generated a smaller coefficient of determination (R^2) than the correlation using percent changes. Second, the expression, change in $P\text{ETCO}_2$/change in $\dot{Q}_T$, was inversely related to the starting $\dot{Q}_T$ ($P < 0.05$). In other words, the decrease in $P\text{ETCO}_2$ for a given $\dot{Q}_T$ decrease was larger at lower $\dot{Q}_T$ ranges. Our method to detect transient non-steady-state changes in $\dot{Q}_T$ by measurement of $P\text{ETCO}_2$ or $\dot{V}\text{CO}_{2[\text{lung}]}$ contrasts with other approaches to determine $\dot{Q}_T$, which apply the Fick principle to measurements of exhaled CO_2 (32–34) during steady state.

In summary, we determined a significant linear correlation of percent changes in $P\text{ETCO}_2$ versus percent changes in $\dot{Q}_T$ of slope 0.73 (Figure 4A). To the extent that these canine data apply to humans, then a change in $\dot{Q}_T$ might be inferred from a change in measured $P\text{ETCO}_2$. For example, a decrease in $P\text{ETCO}_2$ from 35 to 28 mm Hg (20% decrease) could signal that $\dot{Q}_T$ has decreased by 27% (20%/0.73). However, factors other than a decrease in $\dot{Q}_T$ may increase alveolar V_D/V_T and cause a decrease in $P\text{ETCO}_2$. In particular, gaseous and particulate emboli (8,10) or an increase in alveolar pressure (11) can increase alveolar V_D/V_T, widen the gradient between $P\text{ETCO}_2$ and $P\text{ACO}_2$, and limit the clinical usefulness of $P\text{ETCO}_2$ to be a noninvasive estimate of $\dot{Q}_T$. Capnography is already accepted as an important clinical monitor during anesthesia and the measuring equipment is easy-to-use, reliable, and relatively inexpensive (3,35,36). Clinical studies are necessary to determine whether measurements of exhaled CO_2 can provide an on-line, continuous, and noninvasive monitor of cardiac output.

The authors thank Dr. M. F. Roizen for project support, counsel, and review of this manuscript; Dr. Ron Thisted for statistical guidance; and H. Hajyousif for technical assistance.

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Digital Nerve Blocks Can Restore Pulse Oximeter Signal Detection

Denis L. Bourke, MD, and Roger F. Grayson, MD

Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Use of a pulse oximeter for intraoperative monitoring has become virtually a standard of practice in anesthesia (1). Both mechanical equipment failure and peripheral vasoconstriction can cause loss of the pulse oximeter signal (2,3). Without pulsatile capillary blood flow, the pulse oximeter algorithm cannot compute a saturation result. We have found that when, in the face of other indications of normal cardiovascular function, the pulse oximeter fails to detect a signal and the patient's fingers feel cold, volar digital nerve blocks will usually cause a return of normal pulse oximeter function. The brief case reports included in this paper illustrate this point.

For all cases, we measured oxyhemoglobin saturation with a Nellcor pulse oximeter (model N-100C, Nellcor, Heywood, Calif.). We measured fingertip temperatures with an infrared surface temperature scanner (Omega Medical Corp., Clearwater, Fla.). Table 1 shows fingertip temperatures before and after the digital nerve blocks. We report these observations with the permission of our institutional review committee.

Case Reports

Case 1

A 19-yr-old man, ASA physical status I, was undergoing an open reduction and internal fixation of a femoral fracture under isoflurane, nitrous oxide, and morphine anesthesia. The patient had no significant past medical history and was not a smoker. After 4 h of surgery, with oxygen saturation at 100%, the pulse oximeter failed to detect an adequate pulse. Arterial blood pressure was 110/60 mm Hg, heart rate 105 beats/min, and esophageal temperature 37.6°C. Blood loss was less than 500 mL. We performed volar digital nerve blocks on the middle finger using a total of 2 mL of 1% lidocaine. Within 5 min the pulse oximeter began to function on the middle finger but not on the other fingers. Fingertip temperature of the middle finger increased (Table 1). The pulse oximeter continued to function on the middle finger only for the final 2 h of the procedure with oxygen saturation at 100%. Temperatures of the other fingertips did not change significantly.

Case 2

A 62-yr-old man, ASA physical status III, was undergoing a panendoscopy for a tonsillar tumor under general anesthesia with isoflurane, fentanyl, and pancuronium. The medical history included mild hypertension treated with hydrochlorthiazide and a history of smoking 5 cigars per day for more than 35 yr. Shortly after induction of anesthesia, with oxygen saturation at 97%, the pulse oximeter failed to detect a pulse signal in any finger. Arterial blood pressure was 140/90 mm Hg, heart rate was 105 beats/min, and axillary temperature was 35.1°C. We performed volar digital nerve blocks on the middle finger using a total of 2 mL of 2% chloroprocaine. Within 5 min the fingertip temperature increased (Table 1). The pulse oximeter function returned in this finger only and remained for the final 45 min of the procedure with oxygen saturation remaining at 98%. The temperature of the other fingers remained near 24°C.

Case 3

A 52-yr-old man, ASA physical status I, was undergoing a radical retropubic prostatectomy under epidural anesthesia. He had received 20 mL of 0.75% bupivacaine through his epidural catheter and had been given 100 μg of fentanyl and 3 mg of midazolam

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This work was performed at The Johns Hopkins Medical Institutions.

Accepted for publication August 12, 1991.

Address correspondence to Dr. Bourke, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21205-2181.

Reprints are not available.

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0003-2999/91/$3.50

Table 1. Fingertip Skin Temperatures

	Middle finger (°C)		Two adjacent fingers (mean °C)	
Case No.	Before block	10 Min after block	Before block	10 Min after block
1	23.5	29.4	23.5	23.4
2	24.4	27.3	24.1	24.2
3	24.3	30.0	24.4	24.6
4	22.3	25.3	22.2	22.4
Mean ± SD	23.6 ± 1.0	28.0 ± 2.1[a]	23.5 ± 1.0	23.6 ± 1.0

[a] Statistically significant difference from before-block temperature ($P < 0.01$), paired t-test.

intravenously for sedation. The patient was breathing oxygen (6 L/min) via a plastic face mask. The anesthetic level was T-4 bilaterally. After 1 h, with oxygen saturation at 100%, the pulse oximeter failed to detect an adequate pulse. Arterial blood pressure was 105/70 mm Hg; heart rate was 62 beats/min. Blood loss was estimated to be 500 mL. We performed volar digital nerve blocks on the middle finger using a total of 2 mL of 0.5% bupivacaine. Within 10 min, the temperature of the middle fingertip increased (Table 1) and the pulse oximeter function returned in this finger only with oxygen saturation remaining at 100%. The temperature of the other fingers remained unchanged. The pulse oximeter continued to function normally for the final 1.5 h of the procedure.

Case 4

A 72-yr-old man, ASA physical status III, was having a transurethral resection of the prostate with a tetracaine spinal anesthetic. The anesthetic level was T-8 bilaterally. The patient had long-standing hypertension treated with hydrochlorthiazide and a smoking history of 82 pack-years. After 1 h, with oxygen saturation at 96%, the pulse oximeter failed to function on any finger. Arterial blood pressure was 115/55 mm Hg; heart rate was 70 beats/min. Blood loss was estimated to be less than 300 mL. We performed volar digital nerve blocks on the middle finger using a total of 2 mL of 0.5% lidocaine. Within 10 min, the fingertip temperature increased (Table 1) and pulse oximeter function returned on this finger only and remained throughout the remaining hour of the case, with oxygen saturation at 95%. Temperatures of the other fingertips remained near 22.2°C.

Discussion

Since the advent of pulse oximetry, several papers have documented the frequency of unsuspected intraoperative episodes of hypoxemia (4,5). These papers highlight the difficulty of assessing oxyhemoglobin saturation using clinical signs alone. Serious morbidity or mortality can result from relatively brief episodes of arterial hypoxemia. The importance of pulse oximetry is further underscored by studies reporting episodes of serious arterial desaturation during transport to the postanesthesia recovery unit (6,7) as well as in the postanesthesia recovery unit itself (8,9). As a result, the American Society of Anesthesiologists passed an amendment at its 1990 meeting regarding "Standards for Post Anesthesia Care" mandating the same standards for assessing oxygenation in the initial phases of recovery that are now required during the intraoperative period. These new standards take effect January 1, 1992 (standards for postanesthesia care [Approved by House of Delegates on October 12, 1988 and last amended on October 23, 1990]).

When the pulse oximeter output deteriorates or fails, the first priority is to determine by other clinical means the existence of satisfactory respiratory and cardiovascular function. In addition to inadequate capillary pulsations from whatever cause, failure of the pulse oximeter to accurately reflect hemoglobin oxygen saturation may be due to a variety of external or nonphysiologic factors (4,10–12). Although these sources of failure should be considered whenever a pulse oximeter malfunctions, such problems will not be affected by a digital nerve block and therefore will not be discussed here.

Pulse oximeter function requires a pulsating volume of arterial capillary blood between the device's light source and detector (13). An inadequate pulse volume prevents sufficient variation in the transmitted light signal. Without this variation, the pulse oximeter's algorithm cannot compute an accurate value for oxyhemoglobin saturation. A decreased capillary pulse volume can be the result of reduced cardiac output, decreased arterial pulse pressure, intrinsic or extrinsic vascular occlusion, or arteriolar vasoconstriction. It is primarily pulse volume through the monitored capillary bed that is important to oximeter function.

During anesthesia, arteriolar vasoconstriction in the digits is caused most frequently by vasoactive agents, hypovolemia, hypotension, or hypothermia (2,14). Regardless of the cause, if there is sufficient arterial pulse pressure, blocking the sympathetic nerves should cause a local increase in capillary flow and pulse volume. Although it has been shown that satisfactory pulse oximeter signal detection does not inherently imply adequate total flow (15), it seems reasonable to assume that, based on color changes and the increase in the fingertip temperature, the digital blocks effected some improvement in local tissue perfusion in our patients.

The cases described in this report were selected to represent a spectrum of patient characteristics and anesthetic techniques. There is little evidence to suggest that core hypothermia, hypotension, or hypovolemia played a significant role in these cases. All of our patients had fingertip skin temperatures below the normal finger skin temperature range of 26°–31°C. In two instances (cases 2 and 4), the cause may have been related to a history of smoking. A compensatory vasoconstriction above the level of the regional anesthetic block in cases 3 and 4 may have been a contributory factor. Overall, we postulate that in these cases peripheral vasoconstriction was due, in part, to the relatively cold operating room temperatures (18°–21°C). Several authors have demonstrated that despite normal core body temperature, local vasoconstriction and shunting in response to a relatively cold environment can greatly reduce finger blood flow (3,16). In fact, as much as 22% of the population have histories consistent with Raynaud's phenomenon and may be particularly susceptible to cold-induced vasoconstriction (14).

Before performing digital nerve blocks, we attempted other less invasive methods of obtaining a pulse oximeter signal. We tried other accessible sites, and also attempted to increase local perfusion with heat or massage. Although these efforts were occasionally met with short-lived success, they were not suitable for ongoing monitoring.

Each finger is supplied by four neurovascular bundles that provide arterial blood and somatic sensory innervation. Sympathetic innervation is provided by perivascular postganglionic sympathetic fibers. The volar bundles supply the volar half of the finger and all of the finger around the distal phalanx. Therefore, the volar vessels supply the entire area where the pulse oximeter probe is normally placed.

The volar sympathetic nerves can be blocked at the level of the interfinger web. A 25-gauge needle is inserted on either side of the finger just below the surface of the skin, where 1–2 mL of local anesthetic solution is injected. It is not necessary to be excessively precise about needle placement as the structures all lie in a small area of loose tissue between the skin and bone. Vasoconstrictors should not be used as the digital arteries are end arteries. The total volume injected should be less than 8 mL to prevent ischemia from compression. We have not found that a specific local anesthetic agent relates to the success of the procedure; however, we have not explored this issue systematically.

We have used this technique in more than 100 patients. In the face of other clinical evidence of adequate respiratory and cardiovascular function, the digital block failed to restore pulse oximeter function on only seven occasions. There have been no complications. It is important, however, to inform others who will care for the patient that the patient may have a numb finger for some period of time after the procedure.

The pulse oximeter serves as an early warning device that indicates developing desaturation before the appearance of obvious clinical signs that signify the presence of dangerous levels of oxyhemoglobin desaturation. When peripheral vasoconstriction is a contributing cause of signal loss and other noninvasive methods have been unsuccessful, we believe that digital blocks are an effective and safe technique for reestablishing pulse oximeter signal detection. Whenever pulse oximeter information is lost, other, more serious, physiologic causes must first be excluded or treated before turning to digital blocks.

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Asystole After Anesthesia Induction With a Fentanyl, Propofol, and Succinylcholine Sequence

Talmage D. Egan, MD, and John G. Brock-Utne, MD, FFA (SA)

Department of Anesthesia, Stanford University Medical School, Stanford, California

Asystole has been reported after induction of anesthesia with propofol and fentanyl (1). Severe bradycardia has also been reported as a complication of propofol and succinylcholine when used for induction of anesthesia (2). We report a case in which asystole complicated an anesthetic induction sequence consisting of fentanyl, propofol, and succinylcholine.

Case Report

A 42-yr-old woman with a long-standing history of severe rheumatoid arthritis presented for bilateral foot reconstruction of pronounced degenerative bony changes. A detailed medical history revealed, in addition to severe rheumatoid arthritis involving primarily the joints of the hands and feet, a sporadic gastroesophageal reflux problem manifested by dyspepsia. Her rheumatoid arthritis had been severe enough to warrant chronic corticosteroid therapy, and thus she suffered from mild Cushing's syndrome.

She had successfully tolerated numerous general anesthetics in the past, including two uneventful general anesthetics for orthopedic hand procedures in the 5 mo before this admission. These prior anesthetics had included the administration of fentanyl and succinylcholine without untoward effects. Medications on admission included routine doses of flibuprofen, hydroxychloriquine, misoprostol, nizatidine, metoclopramide, triazolam, and prednisone (5 mg/day). The patient also received weekly intramuscular injections of methotrexate. She had no known medical allergies or drug intolerances. The patient was found to be a physically active person without evidence of cardiac, respiratory, renal, hepatic, or neurologic symptomatology.

Physical examination revealed a pleasant, well-nourished, slightly Cushingoid adult woman weighing 70 kg. Heart rate was regular at 72 beats/min and the arterial blood pressure was 125/80 mm Hg. The remainder of the physical examination, including that of the airway, was unremarkable except for obvious bony deformities of the extremities. Preoperative laboratory investigations revealed a hematocrit of 31% and a platelet count of 301,000/mm^3. Because a preoperative electrocardiogram (ECG) had been completely normal 3 mo before, an ECG was not obtained. In view of patient preference and the indeterminate length of the contemplated procedure, the patient gave informed consent for a general anesthetic.

On the day of surgery, the patient took her usual medications including antigastroesophageal reflux drugs with a sip of water. The patient was transported to the operating room without premedication. Upon arrival in the operating room, the patient was given midazolam (2 mg) intravenously. Routine monitoring was instituted. Heart rate was 80 beats/min and the arterial blood pressure was 110/70 mm Hg. While breathing room air, oxygen saturation was 99%.

Before induction of anesthesia, the patient breathed 100% oxygen via a face mask. Over an approximate 5-min period, fentanyl (150 μg) and pancuronium (1 mg) were given intravenously. Heart rate decreased 8–10 beats/min to approximately 70 beats/min.

Hypnosis was then induced with propofol (100 mg IV) and cricoid pressure was applied. After verification of the ability to adequately ventilate via a bag and mask, succinylcholine (100 mg) was administered intravenously. Within 20–30 s after the succinylcholine bolus, the ECG showed an abrupt change from sinus rhythm to asystole. This was confirmed by the lack of a palpable pulse in the radial and carotid arteries, the lack of any ECG lead disconnection, the absence of plethysmographically detected pulsations on the oximeter, and the inability to detect an arterial blood pressure by the automated cuff. At this point, a precordial chest thump was performed without ap-

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Accepted for publication August 16, 1991.

Address correspondence to Dr. Brock-Utne, Department of Anesthesia, Room H3580, Stanford University Medical School, Stanford, CA 94305.

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0003-2999/91/$3.50

parent effect. The period of asystole persisted for approximately 25–30 s according to the ECG monitor. Thereafter a supraventricular bradycardia of approximately 35–40 beats/min was noted. This bradycardia quickly responded to an intravenous bolus of atropine (0.5 mg) given during the asystolic period and heart rate increased to approximately 80 beats/min. Oxygen saturation was 99% upon the return of a detectable pulse, and the arterial blood pressure was noted to be 120/80 mm Hg. Because the period of asystole was brief and the patient's rhythm had spontaneously returned to normal, the anesthesia team was in agreement that the case should continue. The remainder of the anesthetic was uneventful and the patient had an uncomplicated emergence from anesthesia and a smooth postoperative course.

In the postoperative period, the patient was informed of the asystole complicating anesthetic induction and was informed of the potential implications for future anesthetics.

Discussion

Severe bradycardia has been associated with a number of medications used for induction of anesthesia. Fentanyl and other potent opioids are well known for their central vagotonic effect, particularly when given rapidly in high doses (3). Bradycardia is also occasionally observed after the administration of succinylcholine, although this side effect is typically severe only after a second dose of the drug (4). However, asystole after a single dose of succinylcholine has been reported (5). Propofol administration has also been associated with bradycardia (6), although minimal, if any, change in heart rate is more commonly observed. A review of numerous studies investigating propofol's effect on heart rate reveals a wide spectrum of findings with various studies reporting increased or decreased heart rates (7).

In the case reported herein, asystole resulted from the sequential intravenous administration of fentanyl, propofol, and succinylcholine in modest doses. Although the relative contribution of fentanyl, propofol, and succinylcholine to the asystolic episode is unknown, based on the chronology of events, we believe that succinylcholine may have had the most impact on the bradycardia. However, we suspect that this particular combination of drugs, all of which have been individually associated with bradycardia, may have had an additive or synergistic effect in producing the asystole. Previous reports have described severe heart rate slowing or sinus arrest after the sequential administration of propofol-succinylcholine (2), and propopfol-fentanyl (1,8). It is also conceivable that one or more of the patient's concurrent medications could have predisposed to bradycardia, although a review of these drugs indicates that, with the possible exception of metoclopramide, this is unlikely.

Although the mechanisms accounting for the bradycardia associated with opioids and succinylcholine are well described, the mechanism for propofol's possible bradycardia action is not yet clearly delineated. It has been suggested that although propofol preserves baroreflex sensitivity to arterial blood pressure changes, it may act to reset the baroreflex control of heart rate such that slow heart rates are maintained despite the decreased arterial blood pressure usually observed with propofol (9). Propofol may also have a direct effect on sinus node activity (10).

In any case, the bradycardia or asystole associated with fentanyl-propofol-succinylcholine given in sequence can probably be attenuated or prevented altogether by pretreatment with a vagolytic drug such as glycopyrrolate or atropine. Glycopyrrolate effectively mitigates the bradycardic effects associated with fentanyl administration (11). Similarly, atropine premedication has been used successfully to prevent bradycardia associated with propofol-succinylcholine in combination (2). Alternatively, the vagolytic effects of pancuronium can be exploited to prevent the bradycardia associated with fentanyl administration (12). However, pretreatment with pancuronium in our case had no beneficial effect. Finally, succinylcholine can be avoided in favor of nondepolarizing agents unless there is a compelling reason to justify its use (e.g., the rapid onset and short duration of succinylcholine are deemed necessary). The use of a nondepolarizing muscle relaxant in place of succinylcholine is not devoid of heart rhythm side effects, however, as both vecuronium and atracurium have been associated with bradycardia, particularly when given in combination with opioids (13–15).

This case emphasizes the potential dangers of using a combination of bradycardia-inducing drugs for anesthetic induction, and calls attention to the possible beneficial effect of pretreatment with vagolytic drugs in this circumstance. Because the preponderance of evidence now in the literature suggests that propofol generally has minimal effect on heart rate, it is perhaps premature to add propofol to the list of anesthetic medications known to cause bradycardia. We suspect, however, that certain individuals may be susceptible to propofol's possible bradycardia action and that such susceptibility may be augmented by concurrent administration of fentanyl and succinylcholine.

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Intraoperative Pulmonary Edema in a Patient Being Treated With Amiodarone

Andrew K. Satz, MD, Robert K. Stoelting, MD, and Philip S. Gibbs, MD

Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana

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Amiodarone is a potent cardiac antidysrhythmic drug approved for the treatment of recurrent life-threatening cardiac dysrhythmias, recurrent hemodynamically unstable ventricular tachycardia, and recurrent ventricular fibrillation (1). Although amiodarone was originally thought to have very low toxicity, numerous reports have confirmed serious side effects including hepatic dysfunction, low cardiac output syndrome, and pulmonary fibrosis (2–5). There is accumulating evidence that patients treated with amiodarone and undergoing anesthesia with or without cardiopulmonary bypass may be at increased risk for developing postoperative pulmonary complications (6–9). Typically, in those developing amiodarone-induced pulmonary toxicity, the early postoperative period has been uneventful followed in 18–72 h by the onset of dyspnea, tachypnea, arterial hypoxemia, and pulmonary infiltrates requiring prolonged mechanical support of ventilation (6,7,9). This case report is unique in that it describes a patient treated chronically with amiodarone who developed noncardiogenic pulmonary edema within minutes of successful termination of cardiopulmonary bypass.

Case Report

A 41-yr-old, 96-kg man was admitted to the hospital with a history of recurrent ventricular tachycardia resistant to medical therapy that included 400 mg of amiodarone daily and 600 mg of propafenone daily for approximately 6 yr. There was a history of an anterior myocardial infarction in 1984 that was managed medically. Cardiac catheterization revealed two-vessel coronary artery disease and an ejection fraction of 25%. Preoperative pulmonary function tests were forced vital capacity (2.75 L, 51% of predicted), forced expired volume (2.37 L, 55%), and diffusing capacity for carbon monoxide (15 $mL \cdot min^{-1} \cdot mm\ Hg^{-1}$, 39%). While breathing 2 L/min of oxygen by nasal cannula, Pa_{O_2} was 61 mm Hg, Pa_{CO_2} was 40 mm Hg, and pHa was 7.42. The radiograph of the chest revealed cardiomegaly, left upper lobe granuloma, and prominent interstitial markings. Left bundle branch block and first-degree atrioventricular heart block were present on the electrocardiogram.

The patient underwent two-vessel coronary artery bypass graft surgery, ventricular aneurysmectomy, and endocardial resection with cryoablation to a dysrhythmogenic area. Preoperative medication was with morphine, lorazepam, and scopolamine. Anesthesia was induced with midazolam (8 mg IV) followed by a continuous intravenous infusion of sufentanil (1 μg/min) and isoflurane in oxygen as needed for arterial blood pressure control. Skeletal muscle paralysis was provided initially by succinylcholine for tracheal intubation followed by pancuronium to provide paralysis during surgery. Measurements during maintenance of anesthesia but before institution of cardiopulmonary bypass were arterial blood pressure (BP) 125/60 mm Hg, heart rate 60 beats/min, pulmonary artery pressure (PAP) 19/12 mm Hg, cardiac output (CO) 6.1 L/min, Pa_{O_2} 240 mm Hg, Pa_{CO_2} 42 mm Hg, and pH 7.39. Cardiopulmonary bypass lasted 224 min during which time the lungs were exposed to 2-L flows of oxygen and air and 0-cm airway pressure. Mean arterial blood pressure during cardiopulmonary bypass was maintained between 50 and 90 mm Hg with intermittent injections of phenylephrine or administration of nitroglycerin and/or isoflurane.

Cardiopulmonary bypass was easily terminated during the continuous intravenous infusion of sufentanil and dopamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and ventilation of the lungs with oxygen. Initial postcardiopulmonary bypass measurements were BP 80/60 mm Hg, heart rate 90 beats/min (paced because of complete heart block), PAP 28/16, CO 5.7 L/min, hematocrit 25%, end-tidal CO_2 36 mm Hg, and arterial oxygen saturation (Sa_{O_2}) 98%. Total urine output at the conclusion of cardiopulmonary bypass was 1100 mL and intravascular fluid balance was considered to be appropriate.

Accepted for publication August 12, 1991.

Address correspondence to Dr. Stoelting, Department of Anesthesia, Fesler Hall, Room 204, Indiana University School of Medicine, 1120 South Drive, Indianapolis, IN 46202–5115.

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0003-2999/91/$3.50

Total intravenous fluids at this time consisted of 500 mL of plasmanate and 1000 mL of Normosol. Approximately 400 mL of blood had been removed shortly after the induction of anesthesia for subsequent reinfusion after cessation of cardiopulmonary bypass. Within approximately 7 min after termination of cardiopulmonary bypass and before infusion of protamine, pulmonary edema fluid was noted in the tracheal tube. At this time, all previously described measurements remained essentially unchanged except systolic arterial blood pressure that had now increased to 100 mm Hg. Over the next 90 min, approximately 1700 mL of fluid was suctioned from the endotracheal tube utilizing an out-of-line suction catheter. During this time, while the patient was breathing 100% oxygen Sa_{O_2} decreased to between 80% and 85% despite institution of 10–15 cm H_2O positive end-expiratory pressure (PEEP) and intravenous administration of 60 mg of furosemide and 1 g of methylprednisolone. Dobutamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was empirically added to the dopamine infusion although BP, PAP, and CO remained unchanged at this time. Blood loss was replaced as needed with the autologous blood removed before cardiopulmonary bypass. Closure of the sternum was associated with decreases in Sa_{O_2} to 65%–70%, with improvement to approximately 80% when the chest was reopened. For this reason, it was elected to close the skin without approximation of the sternum. Measurements immediately before leaving the operating room were BP 130/70 mm Hg, heart rate 90 beats/min (paced), PAP 28/15 mm Hg, CO 6.2 L/min, Sa_{O_2} 80%, Pa_{O_2} 53 mm Hg (FI_{O_2} 1.0, PEEP 15 cm H_2O), Pa_{CO_2} 54 mm Hg, and pH 7.25.

Postoperatively, cardiac support with inotropic and mechanical (intraaortic balloon) assistance was required to permit continued delivery of high levels of PEEP (15 cm H_2O). The sternum was closed on postoperative day 4. Oxygenation gradually improved during continued treatment with PEEP and diuresis. The trachea was successfully extubated on postoperative day 12. The patient was discharged from the hospital on postoperative day 23.

Discussion

We speculate that the unexpected occurrence of noncardiogenic edema in our patient almost immediately after termination of cardiopulmonary bypass reflected amiodarone-induced pulmonary toxicity. Propafenone, the other drug being administered preoperatively to this patient, is a local-anesthetic type cardiac antidysrhythmic agent that has not been associated with pulmonary side effects. Although we cannot prove a cause-and-effect relationship, there is supporting evidence in the literature for an increased incidence of postoperative pulmonary dysfunction in patients treated chronically with amiodarone (more than 400 mg daily for 20 mo), especially if cardiopulmonary bypass was required (6–8). In retrospect, most patients experiencing postoperative pulmonary dysfunction manifest decreased forced vital capacity, forced expired volume at 1 s, and diffusing capacity and increased alveolar to arterial differences for oxygen preoperatively (4,9). Patients developing postoperative pulmonary dysfunction attributed to amiodarone have typically shown no evidence of left ventricular failure or sepsis and often experience an 18–72-h period after surgery before pulmonary symptoms are manifiest (6). A consistent observation in symptomatic patients is the need for postoperative mechanical support of ventilation, necessitating a prolonged hospitalization. Our patient exemplified many of these characteristics but was unique in the appearance of symptoms almost immediately after separation from cardiopulmonary bypass.

Pulmonary toxicity complicates the course of approximately 5%–7% of patients receiving long-term amiodarone therapy, and mortality may exceed 30% (10,11). The mechanism of amiodarone pulmonary toxicity is not known but could reflect the drug's ability to inhibit lysosomal phospholipase A with the subsequent intracellular accumulation of phospholipids (12). Because of surfactant synthesis, the lungs are the principal organs of phospholipid metabolism, possibly making them susceptible to amiodarone's toxic pulmonary effects. In a perfused lung model, the addition of amiodarone causes pulmonary edema with marked increases in the pulmonary generation of thromboxane and leukotrienes, suggesting an oxidant mechanism (13). It is unproven if amiodarone-induced pulmonary fibrosis in humans reflects oxidant injury although other oxidant drugs such as bleomycin can cause pulmonary fibrosis (14). High oxygen concentrations may lead to the formation of toxic oxidant radicals that oxidize cellular proteins, membrane lipids, and nucleic acids. It is conceivable that the presence of amiodarone in pulmonary tissue leads to increased susceptibility to toxic effects of oxygen.

Clearly, many patients treated with amiodarone undergo anesthesia and surgery without evidence of pulmonary dysfunction (15). Amiodarone-induced pulmonary toxicity may be dose-dependent, as suggested by the report that patients receiving more than 400 mg daily may be at increased risk (8). Some authors have suggested that the risk of elective surgery is increased if the drug-free interval is less than the period of time for which the drug was administered (9). This is an impractical suggestion considering the possible value of amiodarone in patients experiencing potentially fatal cardiac dysrhythmias.

The incidence of noncardiogenic pulmonary edema after cardiopulmonary bypass is low, but when this event occurs, multiple causative factors must be considered. Events previously described to evoke this form of pulmonary edema include (a) distention of the pulmonary vascular bed owing to incomplete decompression of the heart during cardiopulmonary bypass, (b) activation of the complement pathways, which is more likely with a bubble than membrane oxygenator, (c) transfusion-related reactions most likely reflecting leukocyte antibodies, (d) allergic reaction to protamine, and (e) sepsis (16–19). None of these events seem to be likely precipitating factors in our patient. For example, distention of the pulmonary vascular bed did not occur (as reflected by monitoring of cardiac filling pressures), the pump prime did not contain blood products, a membrane oxygenator and 20-μm filter were used, and pulmonary edema was manifest before the infusion of protamine was initiated. An increase in extravascular fluid volume reflecting an increased permeability to proteins after 2 h of normothermic cardiopulmonary bypass in the dog has been described (20,21). Cardiopulmonary bypass often exceeds 2 h in our institution, but noncardiogenic pulmonary edema or evidence of increased lung water does not occur. Nevertheless, cardiopulmonary bypass in the described patient was prolonged (224 min) and a possible role of this factor, perhaps being accentuated by underlying amiodarone-induced lung damage, cannot be excluded.

In the absence of a known mechanism for amiodarone-induced pulmonary toxicity, rational guidelines cannot be developed for the management of these patients during anesthesia and surgery. The parallels with bleomycin are obvious, but a similar toxicity has not been confirmed such that recommendations to minimize crystalloid infusion and to limit inspired oxygen concentrations to the minimum level necessary to maintain arterial oxygenation are entirely speculative. In fact, evidence that hyperoxia enhances bleomycin-induced pulmonary toxicity has not been a consistent observation (22,23). Nevertheless, excessive intravascular administration of fluids and the possible irritant effect of excessive concentrations of oxygen probably should be avoided in patients being treated with amiodarone who show evidence preoperatively of drug-induced pulmonary toxicity.

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Letters to the Editor

A Simple Test for Scopolamine Mydriasis

To the Editor:

In reference to the letter by Dr. Kiyama (1), it should be noted that butylscopolamine is a muscarinic blocker and produces mydriasis at the neuromuscular junction of the iris sphincter and not at the ciliary ganglion. Because this receptor can be affected by topical drugs, inadvertent hand delivery can often account for unilateral effects (2). There is a useful test to differentiate scopolamine mydriasis from central nervous system pathology (third nerve palsy). Pilocarpine eye drops (0.5% or 1% solution) can be readily obtained from the hospital pharmacy. Topical administration of pilocarpine will not constrict the mydriatic scopolamine-blocked pupil, whereas if the pupil is dilated because of central nervous system pathology, pilocarpine will rapidly constrict the pupil (3,4).

Merlin D. Larson, MD
Department of Anesthesiology
University of California, San Francisco
521 Parnassus Avenue
San Francisco, CA 94143-0648

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In Response:

I appreciate Dr. Larson's interest in my report (1). I apologize for being incorrect in stating that butylscopolamine produces dilated pupils at the level of the ciliary ganglion, when in fact it acts at the peripheral neuromuscular junction of the iris sphincter, as Dr. Larson clearly mentioned. It seems very interesting to consider inadvertent topical delivery of butylscopolamine as a probable cause of anisocoria in my patient. But in my case, butylscopolamine was drawn into the syringe from the ampule and my fingers were not exposed to the drug as they might be in the case of cycloplegia from transdermal scopolamine (2). It is my routine clinical practice to check pupils intermittently, usually every 30 min during general anesthesia, and between those examinations the eyes are firmly taped shut. Therefore, it is unlikely that the left pupil was inadvertently contaminated with butylscopolamine. I agree with Dr. Larson that topical administration of pilocarpine eye drops is an inexpensive, easily applicable test for differential diagnosis of fixed, dilated pupil (3). But it still remains unclear why systemically administered anticholinergics could have caused unilateral mydriasis.

Shuya Kiyama, MD
Department of Anesthesiology
Saiseikai Yokohama-shi Nambu Hospital
3-2-10, Konan-dai, Konan-ku
Yokohama, 233 Japan

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Aseptic Closed System for Injections Through Continuous Spinal Catheters

To the Editor:

The advent of small-gauge continuous spinal catheter kits has greatly facilitated the implementation of this very useful technique (1). Of concern to many practitioners, however, is the risk of infection associated with frequent opening and closing of the catheter system for repeated injections of local anesthetics in the operating room or for titration of postoperative analgesia in the postoperative anesthesia recovery area. We describe a simple system that allows repeat injections through continuous spinal catheters using an aseptic closed-system technique.

The materials used include a continuous spinal catheter kit, a three-way Luer lock stopcock, and a 5- or 10-mL syringe, all of which are readily found in most anesthesia departments (Figure 1).

After placement of the continuous spinal catheter, the Tuohy Borst adapter is placed at the distal end in the usual fashion. The Luer plug is discarded, and a sterile three-way Luer lock stopcock is attached to the Tuohy Borst adapter. This allows placement of a sterile reservoir syringe and the smaller dosing syringe found in most continuous spinal catheter kits. By turning the stopcock, the syringe used for injection may be filled from the reservoir syringe with the desired volume of local anesthetic. Another turn of the stopcock allows injection of this dose from the small syringe (Figure 2).

In our experience, the addition of the stopcock adds negligible resistance to this system and allows repeated injections with maintenance of sterility. The small gauge of the spinal catheter makes injection of the system difficult

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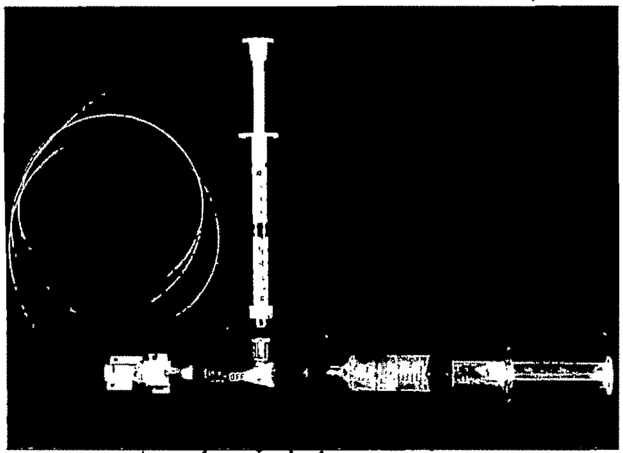

Figure 1. Components of the closed, continuous spinal catheter system. The components are the continuous spinal catheter with the Tuohy Borst adapter, a 1-mL syringe with a Luer connector, and a 5-mL reservoir syringe containing the local anesthetic. The components are opened and assembled under sterile conditions.

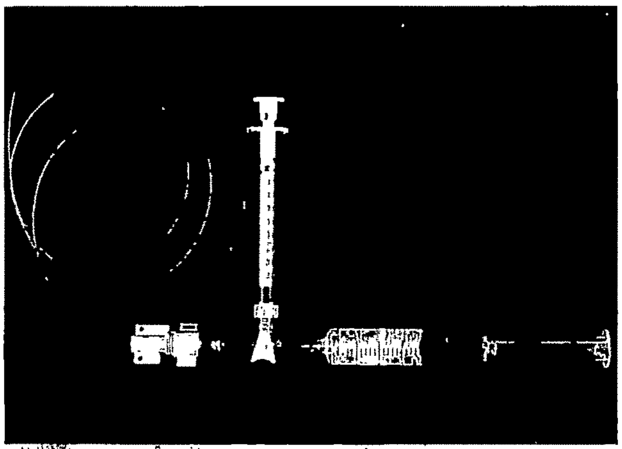

Figure 2. The assembled components of the closed continuous spinal catheter system. By turning the Luer stopcock, local anesthetic can be directed from the large reservoir syringe into the dosing syringe. By turning the stopcock again, a measured dose can be administered from the dosing syringe. Drug should not be given directly from the reservoir syringe owing to the resistance of the small catheter.

with a syringe larger than a 1-mL syringe. Our modification provides for repeated injections, provides a reservoir for additional drug using a 5- or 10-mL syringe, and allows sterility to be maintained by assembling the components under sterile conditions while the continuous spinal catheter is being placed within the subarachnoid space. We have had no complications with this technique nor with microspinal catheters in general.

George A. Arndt, MD
Heidi Klessig, MD
Department of Anesthesiology
University of Wisconsin Clinical Science Center
B6/387 UW CSC
600 Highland Avenue
Madison, WI 53792

Reference

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Manufacturing Defect in a Double-Lumen Tube

To the Editor:

We recently unexpectedly encountered a manufacturing defect in a double-lumen endobronchial tube that, had it gone unrecognized, would have resulted in complete inability to evacuate secretions from the tracheal lumen and right lung. We would like to alert other anesthesiologists to this occasional manufacturing defect.

After induction of general anesthesia for a patient requiring thoracotomy, a 39F endobronchial tube (Broncho-Cath, Mallinckrodt, Argyle, N.Y.) was positioned in the usual fashion. Checking breath sounds before and after clamping each lumen indicated correct tube position. However, when an attempt was made to confirm proper placement using a pediatric fiberoptic bronchoscope, it was discovered that the tip of the bronchoscope could not be advanced into the tracheal lumen more than a few centimeters before encountering an obstruction. The bronchoscope was therefore removed and the endobronchial tube was changed. Anesthesia and surgery proceeded uneventfully.

Inspection of the defective endobronchial tube revealed that the obstruction resulted from a semicircular protrusion from the plastic tube wall. To demonstrate the protuberance, the tube was radiographed (Figure 1). The tube was

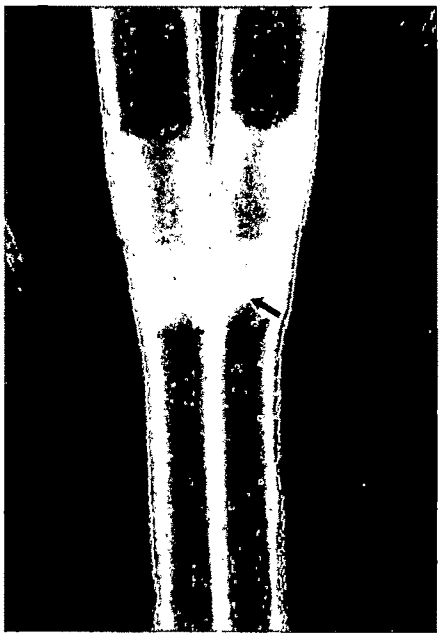

Figure 1. Radiograph of the defective double-lumen tube. *Arrow* points to obstruction in tracheal lumen.

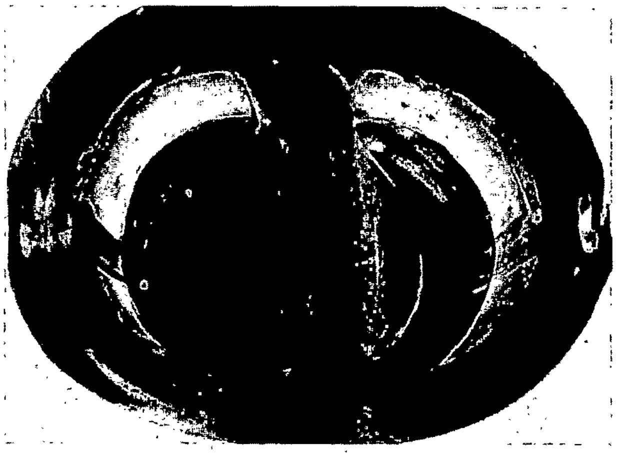

Figure 2. Cross section of the defective double-lumen tube showing obstruction in the tracheal (*right*) lumen.

then cut in cross section just above the level of the obstruction and photographed (Figure 2). The manufacturer was immediately notified of the defect, and they have stated that quality control has been upgraded to prevent this problem in the future.

A computerized search of the medical literature revealed no similar reports in the English language, but there was one report of five similar cases from Germany (1). In those cases, also involving Mallinckrodt Broncho-Caths, the presence of the obstruction was only discovered intraoperatively when even a very small catheter could not be introduced into the tube lumen for aspiration of bronchial secretions. In the German cases as in ours, the obstruction occurred near the point where two separate tubes are joined to form a single double-lumen tube.

Inability to suction bronchial secretions from the lumen of an endotracheal or endobronchial tube can have extremely serious consequences, especially if they obstruct ventilation. Perhaps no further double-lumen tubes with the above-described defect will be sold. However, the fact that other such tubes may still be among those already in stock in anesthesia departments suggests that it is prudent to verify patency of both lumens of an endobronchial tube visually or with a bronchoscope or suction catheter before using it in a patient.

Carol Campbell, MD
Susheela Viswanathan, MD
James M. Riopelle, MD
M. Naraghi, MD
Department of Anesthesiology
Charity Hospital of New Orleans
1532 Tulane Avenue
New Orleans, LA 70140

Reference

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Reinserting a Catheter Into a Single-Use Adapter: A Safe and Cost-Effective Method

To the Editor:

Utilization of a Continuous Spinal Anesthesia Tray (Kendall Healthcare Products Company, Mansfield, Mass.) has made the technique of delivering incremental doses of local anesthetic and preservative-free narcotic into the subarachnoid space increasingly popular. The tray includes an adapter that has a compression fitting with a silicon bushing. Once compressed, the bushing does not permit the catheter to be reinserted. A common, frustrating problem associated with the product is the inadvertent disconnection of the catheter from the adapter.

A means of overcoming this problem is to loosen the compression fitting and insert a sterile 22-gauge spinal needle retrograde through the fitting. The stylet is then removed and the catheter is passed into the needle (Figure 1). The needle is removed, and the fitting is tightened again to secure the catheter. When the catheter is replaced by this method, no leakage occurs. The method is effective, and the cost of opening a new tray can be avoided.

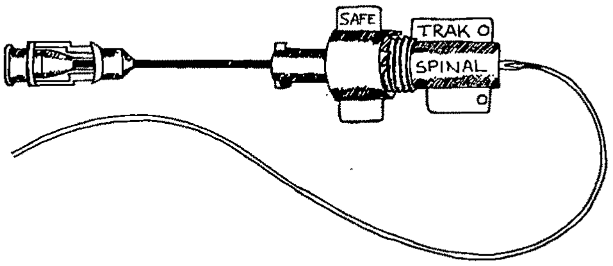

Figure 1. A 22-gauge spinal needle permitting the catheter to pass through the silicon bushing of the adapter.

Gary Kirchhoff, MD
Ron Stillwell, CRNA
Department of Anesthesiology
University of South Florida College of Medicine
12901 Bruce B. Downs Boulevard, MDC59
Tampa, FL 33612-4799

Use of an Oxygen Concentrator Linked to a Drawover Vaporizer

To the Editor:

Drs. Jarvis and Brock-Utne (1) have reintroduced us to a modern version of the drawover anesthesia system (PAC Unit, Ohmeda). As military anesthesiologists we are aware of this apparatus and its potential use under austere conditions. Until now information concerning this equipment has been concentrated in the British anesthesia literature and in journals directed toward physicians practicing in developing nations (2–4).

We are troubled by two of the authors' recommendations. First, they recommend a 900-mL Oxygen Economizer Tube (OET). This translates into 2 m of standard tubing, a cumbersome addition to an otherwise compact piece of equipment. Previous studies have shown that a much smaller OET is adequate (150–350 mL) (2–4). The standard OET supplied with the PAC Unit is 33 cm and 130 mL.

Second, the authors recommend changing the FDA labeling for the PAC to allow its use in humans for training purposes. This is probably unnecessary and perhaps is inappropriate. The PAC Unit like other drawover systems is very simple in design. Assembly of the equipment is straightforward. The vaporizer output is proportional to the setting on the dial.

The difficulty arises not from the equipment, but from the inhalational anesthetic technique utilized with this equipment, which is now foreign to a generation of anesthesia providers. Today's "balanced technique," combining nitrous oxide, low-dose isoflurane, a myriad of intravenous agents, muscle relaxants, and mechanical ventilation, is not applicable to the drawover apparatus.

However, inhalational techniques suitable for drawover devices can be practiced with conventional anesthesia equipment. By omitting nitrous oxide and utilizing spontaneous or manually controlled ventilation, the anesthesiologist can gain (or regain) familiarity with inhalational techniques. If air/oxygen mixtures with fresh gas flows of 8–12 L/min are used, the system will be nonrebreathing and the response to changes in the vaporizer setting will simulate use of the drawover system. Using familiar equipment and monitors to simulate the drawover apparatus is preferable as, at any time, the anesthesiologist can easily revert to a more accustomed technique.

In our opinion, training requires a twofold approach: (a) practicing inhalational techniques with standard equipment, and (b) periodic, didactic familiarization with the drawover apparatus. This should provide sufficient preparation in the unlikely event that an anesthesia provider may actually require the use of this equipment.

Charles P. Kingsley, MD
Department of Clinical Investigation and
Anesthesia & Operative Service

R. K. Baumgarten, MD
Anesthesia & Operative Service
Department of Surgery
Brooke Army Medical Center
Fort Sam Houston, TX 78234-6200

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The authors' opinions do not purport to represent official views of the Department of Defense.

In Response:

We are grateful to Drs. Kingsley and Baumgarten for their interest in our article. We also believe that the inhalational anesthetic technique, especially using this equipment, is now foreign to a generation of anesthesia providers. Therefore, our objective was to evaluate an oxygen concentrator linked to a drawover vaporizer.

It is important to make two comments regarding factors that determine the volume of the OET.

1. The OET is designed to accumulate the oxygen that flows from the oxygen source during the period when inspiration does not occur. The volume of tubing required to accommodate this depends on the oxygen flow from the oxygen source, and the period for exhalation. At a flow rate of 5 L/min from the oxygen concentrator, a volume of 900 mL is filled in 10.8 s. With streamlined flow, some oxygen may be lost from the tube in a period of less than 10.8 s. Periods of 10 s between inspiratory phases are possible with a ventilation rate of about 5 breaths/min.
2. The other factor is the tidal volume. If the tidal volume used is always less than the volume of the OET, then the oxygen will not be diluted due to insufficient volume of the OET.

For these reasons, we used a volume of 900 mL, so that we could test the performance of the apparatus under a wide range of respiratory parameters. It did indeed perform as expected.

In King et al.'s paper (1), they used a maximum oxygen flow of 2 L/min and a constant respiratory rate of 17 cycles/min. As they explain, with an expiratory phase of 1.76 s, the maximum amount of oxygen accumulated during this time would be 59 mL, less than the volume of their corrugated reservoir (OET) tube (150 mL).

If one were to always use a tidal volume less than the volume of the OET, or use an OET of volume greater than that needed to accumulate the maximum flow of oxygen used during the expiratory period, then there should be no significant degradation in performance vis-à-vis the expected oxygen concentration delivered by the apparatus at the particular respiratory parameters. This may well permit the use of an OET smaller than 900 mL. However, we did not test this specifically in our study. Rather, we showed that under a wide range of respiratory settings, the apparatus will perform satisfactorily with an OET of 900 mL.

Furthermore, in the diagram supplied by King et al., it is not surprising that the reservoir bag did not fill, as the tube is open to the atmosphere. It is necessary to use a hollow tube rather than an expandable bag, unless one incorporates a valve on the air inlet end of the OET. The valve should permit air inflow at very slight negative pressures (so that the reservoir bag is emptied first), and should also permit spill of oxygen at very slight positive pressure should the reservoir bag become full. This solution may keep the apparatus more compact, but we believe it would detract from its intrinsic simplicity and safety.

Finally, we believe that the drawover anesthesia system (PAC Unit, Ohmeda) is a useful anesthetic technique, not only for military use, but in many other situations when conventional equipment is not available, either temporarily or permanently. Hence we strongly recommend that the PAC Unit be allowed to be used in humans also in the United States, especially for training purposes.

David Jarvis, MD
Department of Anesthesia
Royal Adelaide Hospital
Australia

John G. Brock-Utne, MD, FFA (SA)
Department of Anesthesia
Stanford University Medical Center
Stanford, CA 94305

Reference

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Monitoring Bilateral Breath Sounds

To the Editor:

We read with interest the letter by Lee (1) in which two precordial stethoscopes are joined at a stopcock and attached to an earpiece. This is to call to your attention an earlier description of an identical model by Schwartz (2).

Since the publication in 1987, we have continued to successfully utilize this simple device in a variety of surgical cases with difficult access to the chest, as well as in situations when lung isolation is required. We have found the system particularly useful in neonates and small infants because of their short trachea and consequent high risk for endobronchial intubation.

Nathan Schwartz, MD
Department of Anesthesiology
Albert Einstein Medical Center
York and Tabor Roads
Philadelphia, PA 19141

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In Response:

At the time of writing my description of the double precordial stethoscope assembly, I was unaware of the existence of Dr. Schwartz's Letter to the Editor. Therefore, I would like to apologize to him.

A Medline literature search employing "Precordial stethoscope" and "Respiratory monitoring" as key words, failed to reveal any prior description of this model. The fact that the advantages reported by Dr. Schwartz and myself correlate, attests to the usefulness of this model.

Edward Lee, MB, BCh, FFARCSI
Department of Anesthesiology
Vanderbilt University Hospital
Nashville, TN 37232

URI or Preoperative Obstruction?

To the Editor:

I believe the argument about the significance of preoperative upper respiratory tract infection (URI) in children has only been clouded by the recent contribution by Cohen and Cameron (1). The problem is that children with preoperative upper respiratory obstruction and no other medical problem were labeled "URI" and are the probable source of the perioperative respiratory problems in the "URI" group.

Their results are derived from a database in which the anesthesiologist seems to have only a yes/no option to describe the presence of *any* upper respiratory problem (URP). In an attempt to isolate URI patients, they only analyzed patients with URP without any other medical problem. Validation of this approach involved 100 charts from the URP group, of which 53 fulfilled the URP-alone criterion. Of these 53, four patients did not have URI (2 laryngeal web and 2 stridor).

The authors suggest that this is a small number of misclassified cases and "unlikely to affect the final results." This 4 of 53 represents about 7%. They all represent patients with preoperative upper respiratory obstruction without URI who would be treated in the analysis as URI patients. This 7% would neatly explain the entire difference between the nominal "URI" group and those without URI. They would certainly be likely to have continuing obstruction intraoperatively and postoperatively.

This database has been a source of several excellent papers in the past. Unfortunately, it appears this attempt to get more out of the computer than went in and its subsequent publication has produced a "landmark paper" on preoperative URI, which, with review of the 1283 charts, may well be based on data showing that children without URI but with preoperative upper respiratory obstruction commonly have intraoperative and postoperative obstruction.

Ian McKenzie, MBBS, FFARACS
Department of Anaesthesia
Royal Children's Hospital
Parkville, 3052
Victoria, Australia

Reference

1. Cohen MM, Cameron CB. Should you cancel the operation when the child has an upper respiratory tract infection? Anesth Analg 1991;72: 282–8.

In Response:

Dr. McKenzie's letter raises the question about misclassification bias: that is, can the results found in the article be accounted for by "contamination" of the URI group with children who did not have a URI?

In our study, the anesthesia follow-up reviewer would record events if they were "new" or if they were unexpected. If a child with "stridor" was undergoing an operation to explore the reason for the stridor, then this would not have been considered a new complication and would not be captured in the database (that is the reason the operation was not considered an "adverse event"). Therefore this does not explain the results.

In our chart review, we found that of 53 children who were classified as having a URI and no other problem, 2 children had stridor and 2 children had laryngeal web. This rate roughly translates as 7.6%. If this rate is applied to the URI group, then approximately 98 children did not have a URI. The question asked is this: could the poor outcomes among these approximately 98 children account for all the adverse events found in the study? There are two factors to consider here. First, are the numbers large enough to account for the differences, and second, does this make sense biologically or clinically?

To examine the first factor, let us consider two examples from the paper, which are shown in Table 2. The rate of intraoperative airway obstruction was 3.43% in the URI group and 0.76% in the comparison group. The excess risk (rate in the URI minus rate in the non-URI group) would be 3.43% − 0.76% = 2.67%. The rate in the true URI children (1283 − 98 = 1185 children) should be the same as the non-URI children at a rate of 0.76%. The number of children in the true URI group having intraoperative airway obstruction would be 1185 times 0.76% or 9 children. Therefore to achieve an overall rate of 3.43%, the 98 misclassified children would have to account for the remaining 2.67% excess risk. Therefore 35 (44 − 9 children) in the misclassified group would have to have had airway obstruction. This would mean a rate of 35 divided by 98 = 36% of the misclassified children would have to have airway obstruction. A second example would be postoperative "other respiratory" events. Here the rate among the misclassified children would have to be 72% to account for the excess risk. It is unlikely that the rates among the misclassified children would be this high. So although the number of misclassified children appears large, it is not large enough to account logically for the excess risk.

In addition, it is extremely unlikely that the majority of misclassified children did in fact have the rare condition of laryngeal web; they were more likely to have a variety of other conditions. As well, there should be no biological reason why these children would be at higher risk for problems with temperature regulation, whereas it should make a lot of sense that children with URI might have difficulties.

However, the definitive answer to Dr. McKenzie's query would involve a review of the charts where an adverse respiratory event took place. This we will endeavor to do.

Marsha M. Cohen, MD, FRCPC
Clinical Epidemiology Unit, Room A443
Sunnybrook Health Science Centre
University of Toronto
A4, 2075 Bayview Avenue
North York, Ontario
Canada M4N 3M5

Safety of Alcohol After Midazolam

To the Editor:

There is one important omission in the study of Lichtor and colleagues reported in the May 1991 issue (1). In a pharmacokinetic study of more than 217 patients given 0.3 mg/kg of midazolam IV, we found a 6% incidence of a prolonged elimination half-life (2). There was a very marked effect with prolongation from the normal 3–3.5 h (range 0.8–6.6 h) to a range of 8–22 h. None of our subjects had received any benzodiazepines for 2–3 days before the study, yet in 14 we detected midazolam in the blood 24 h after administration. All of these had an abnormal half-life.

Although the likelihood of any interaction between residual midazolam and alcohol is small, with a 1:20 probability of a prolonged action, patients should be warned of this possibility. The seeming dismissal of it by Dr. Lichtor and colleagues is probably rash, particularly as it may have serious medicolegal implications.

J. W. Dundee, MD
Department of Anaesthetics
The Queen's University of Belfast
Belfast, Northern Ireland

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In Response:

Dr. Dundee raises an important point that may not have been entirely clear from our paper (1): alcohol use should be discouraged after any sedation, including that which involves midazolam. It is also very important for patients postoperatively to refrain from driving and operating machinery. However, from our study results, we still suggest that sedative drugs such as midazolam have no apparent residual effects that would enhance the effects of alcohol consumed several hours after sedation. Also, the dose of midazolam we used was one-third that described in his paper (2), and even at that dose, Dr. Dundee concluded that the findings were probably of no clinical significance. Blood levels of benzodiazepines may also not correlate with impairment in psychomotor function. For example, Dr. Dundee reports that the normal elimination half-life of midazolam is 3–3.5 h (range 0.8–6.6 h); yet, in our study, by 3 h for the majority of psychomotor tests, and by 5 h for the remainder, we could find no evidence of impairment.

In our study, we examined volunteers younger than 35 yr of age. In the discussion section of our paper, we stated that when patients are older and are to receive other drugs, our results may not be applicable. Certainly, further work with other drugs and other drug combinations is warranted.

J. Lance Lichtor, MD
James Zacny, PhD
Kari Korttila, MD, PhD
Jeffrey L. Apfelbaum, MD
Department of Anesthesia and Critical Care
The University of Chicago
5841 South Maryland Avenue, Box 428
Chicago, IL 60637

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The International Anesthesia Research Society Seal

To the Editor:

We read with great interest the editorial explaining the changes in format *Anesthesia and Analgesia* has undergone with the changing of the editorial guard. We applaud the new cover, with the great seal of the Society displayed prominently on it. Alas, we could find no explanation for the symbols displayed. After some research we have found the following explanation.

With the emergence of the International Anesthesia Research Society from the National Anesthesia Research Society in 1922 (1), Dr. Francis Hoeffer McMechan, the founder, created the logo in an attempt to pictorially describe the Society's mission. The central figure, a lady, is said to represent medical science; however, she bears a strong resemblance to the traditional countenance of Athena, the Greek goddess of knowledge. The lamp upon a pedestal symbolizes the search for knowledge, or perhaps, the illuminating light for the books, sources of knowledge, in the foreground. The owl represents wisdom; the ivy leaf truth. The globe portrays the worldwide nature of the Society (2). The motto, "We Strive Always for the World Conquest of Pain," was the common theme in anesthesia circles during the 1920s.

It is our hope that this explanation is of some help to the readership of the Journal. Moreover, a short paragraph on the inside front cover explaining the seal may add to the striking changes in cover design.

Douglas R. Bacon, MD
Mark J. Lema, PhD, MD
Department of Anesthesiology and Critical Care Medicine
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263

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Implications of Lethal Anesthetic Doses

To the Editor:

The article by Ghantous et al. (1) suggests that 1.9–2.2 mM desflurane and 2.3 mM isoflurane decrease the potassium content of slices of liver from guinea pigs. A concentration of 1.1 mM desflurane did not produce a change.

The meaning of these findings is complicated by the concentrations used. The preparation applied by Ghantous et al. bathed the slices at 37°C in a Krebs-Henseleit buffer that has solvent properties probably equal to those of saline. Given the assumption of similarity to saline and a knowledge of the saline/gas partition coefficient for desflurane (0.225) (2) and Krebs' solution for isoflurane (0.55) (3), the partial pressures exerted by these concentrations may be calculated. For desflurane, a concentration of 1.9–2.2 mM provides a partial pressure of 21%–25% of an atmosphere, well beyond any partial pressure that might be applied in practice (or that would be survived by an animal or human). A concentration of 1.1 mM gives a partial pressure of 12% or about twice the MAC (4). Similarly, 2.3 mM isoflurane provides a partial pressure of 10.6% of an atmosphere, or about 14 times MAC (5).

Given the high concentrations applied, what conclusions can be drawn regarding the toxicity of either desflurane or isoflurane? If the effects were proportional to concentration, one might argue that the higher concentrations revealed effects that lower concentrations would have revealed if a larger sample had been used. However, the data supplied by Ghantous et al. suggest an "S-shaped" curve with little effect at concentrations within the clinical range. Thus, it would appear that the phenomenon reported applies only to lethal anesthetic partial pressures. The relevance to pressures used in practice is unclear.

Edmond I. Eger II
Department of Anesthesia
University of California
P.O. Box 0464, Room S-455
San Francisco, CA 94143

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Methods Comparison in Clinical Observational Studies

To the Editor:

In their comparison of a new intravascular blood gas monitor with a conventional analyzer, Barker and Hyatt made two major assumptions in their statistical analysis that were not mentioned in their paper (1).

First, in pooling the data from their 14 patients, they implicitly assumed that the functional relationship between the measurements was identical for each subject (and thus for each optode sensor) tested. We found this not to be the case in our own evaluation of a similar fluorometric instrument intended for sensing in the cardiopulmonary bypass circuit (2). Our finding of statistically significant differences between the regression lines among patients suggested that important differences between sensors occurred in manufacturing, calibration, or the individual patient's interaction with the sensors.

We appreciate the methodologic difficulties encountered in forming regressions of data from individual patients to assess instrument performance. As the variables of interest often cannot be manipulated explicitly, the values observed from particular patients may be clustered, resulting in a degenerate situation where a single extreme value may grossly affect the line-fitting for those patients. Additionally, it is rarely possible to acquire an adequate number of data points from one patient to cover the full operating range of the instrument. Nevertheless, statistical comparison of the regression lines among patients remains a valid method by which to determine whether significant between-patient error exists (3).

Although Barker and Hyatt stress the virtues of Altman and Bland's technique of analysis over linear regression, careful reading of the original statistical references (4–6) shows that those authors consider both their technique and regression to be acceptable approaches to method comparisons. Given that Barker and Hyatt chose the Altman and Bland analysis, the validity of data pooling should have been tested by repeated measures analysis of variance (4,5). However, this would have required equal numbers of measurements to be taken at the same predetermined epochs for each patient. Alternatively, the results of separate analysis for each of the 14 patients (including the range of values observed) could have been presented to the reader for descriptive comparison. As it is, the reader has been left to wonder whether between-patient variability was an important factor in the reported results. The limits of agreement calculated from the pooled data will be a pessimistic estimation of variability relative to the within-patient estimates. Also, the clinician is not interested in the confidence limits of a large sample of measurements over a number of patients but rather would like to know the range of agreement expected for the individual patient or even for a single measurement.

The other assumption not mentioned by the authors is that estimation of accuracy and precision requires prior testing for proportional error. If the agreement shows dependency on the magnitude of the measurement (as is evident for $Paco_2$ in their Figure 4B), estimates made without appropriate data transformation may be misleading.

Finally, the issue of calibration drift in other studies is raised, yet the authors fail to address it in their own work. Scatterplots of the bias as a function of time would have allowed assessment of the dependency of accuracy on time from sensor insertion.

Although methods comparison studies are difficult to perform in a clinical setting, it is important that new instruments be assessed in their actual working environment. Thorough analysis of the data may uncover useful information about the sources of error and about how to improve instrument performance.

Michael L. Nessly, BS
G. Bashein, MD, PhD
Department of Anesthesiology
University of Washington
Seattle, WA 98195

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In Response:

Drs. Nessly and Bashein raise some valid points regarding the difficulties of performing a methods comparison study in the clinical setting. However, the use of pooled data for multiple subjects does not "assume" that there are no differences between sensors or their interactions with the patients. Pooling of data does in fact combine between-subject variability and within-subject variability, so that the two cannot be distinguished by the results shown in our paper. Drs. Bashein and Nessly used the same procedure in their original abstract describing fluorometric monitoring during cardiopulmonary bypass (1). In their later paper on the same study, they presented individual linear regression data on 16 separate sensors, showing the degree of scatter between the various regression lines (2). We have performed the same analysis on our own data, and concluded that the results do not contribute significantly to the impact of the paper but only add to its complexity. As Altman and Bland state in their article on methods comparison studies, linear regression, like correlation, is strongly dependent on the range of values covered by the data (3). That is, in subjects for whom the data tend to cluster in a small region of the scattergram, the correlation will be low and the regression slope and intercept values will be meaningless. In our own data, the regression slopes for individual pH sensors vary from 0.3 to 1.7 (mean 0.87, SD 0.48). This wide variation merely reflects the fact that pH values for a given individual changed relatively little during the course of the operation. On the other hand, the pooled pH data (Figure 3A and Table 1) span a reasonable range of values and yield a regression line not far from the line of identity (4).

The use of pooled data has both advantages and disadvantages. Although it does confound the influences of between-subject and within-subject variability, pooled data may be the only means to obtain a satisfactory range of the variables being measured in a clinical study. This important point is also stated in the third paragraph of the letter above.

Although authors may disagree as to which statistic best represents the data, one fact is clear: none of these statistics is useful without the raw data from which the reader may draw his own conclusions. We have accordingly presented our raw data in both scatterplot and bias-plot format, as recommended by Altman and Bland (3). As Drs. Nessly and Bashein have noted, these plots suggest a degree of proportional error (see Figures 4b and 4c) (4). This proportional error led us to present the so-called "percent-bias" and "percent-precision" for the pooled data in Table 1. These are the mean and standard deviation of the percentage differences between the measurements. Note that if we did not study the pooled data, the proportional nature of the error would not have been apparent.

To conclude, the prospective user of this new monitor needs the answers to two questions: (a) How accurate are the absolute values given by this device? (b) How well does the device follow trends in a given individual? These two questions have not been separated in our paper because of the practical limitations of our clinical investigation. By combining between-subject and within-subject error, pooled data may provide a more pessimistic outlook than single-subject data. Nevertheless, we argue that this is often more appropriate than providing individual linear regressions that may be meaningless because of the clustering of the single-subject data. In a device subject to both types of error, we have chosen to present the data in a format that shows the influences of both.

Steven J. Barker, PhD, MD
Department of Anesthesiology
UCI Medical Center
101 City Drive South
P.O. Box 14091
Orange, CA 92613-4091

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Section Editor
Norig Ellison

Book Reviews

Mechanical Ventilation and Assisted Respiration: Past, Present, and Future

A. Grenvik, J. Downs, J. Räsänen, and R. Smith, eds.
New York: Churchill Livingstone, 1991, 190 pp, $85.00.

This book is the first volume of a new series *Contemporary Management in Critical Care* edited by Drs. Tobin and Grenvik. Appropriately, the first issue is entitled *Mechanical Ventilation and Assisted Respiration.* Intensive care units were initially developed because of the need for long-term mechanical ventilation. Although techniques for mechanical ventilation appeared to have reached their ultimate plateau over a decade ago, recent studies have suggested that alternatives in ventilatory support may decrease lung injury and the adverse hemodynamic effects of mechanical ventilation. The book is primarily oriented toward presenting these new developments. Thus, 6 of the 10 chapters deal with high-frequency ventilation, pressure-support ventilation, airway pressure-release ventilation, extracorporeal carbon dioxide removal, extracorporeal membrane oxygenation, and current trends and future goals in the management of life-threatening respiratory failure. The remaining four chapters cover evolution of mechanical ventilation; flow, pressure, and time modifications; weaning problems; and hemodynamic effects of mechanical ventilation. Each chapter is written by recognized experts in that specific area and presents a concise but comprehensive view of the subject. The chapters are uniformly current with many references from the years 1988 to 1990. The chapters are easy-to-read and presume little prior knowledge of the area. In the preface, the editors state "the book should be of particular interest not only to subspecialty physician trainees in critical care medicine, but also to house-officers and senior medical students on ICU rotation and to dedicated ICU nurses and respiratory therapists." I believe the book will be valuable for such an audience, but that the full-time intensivist will wish for more detail. Although the chapters at first appear to be of average length, only half of the width of the page is used for text and the otherwise excessively wide margins are used to reproduce in bold print one or two sentences of text per page. This format is presumably used to direct the reader's attention to significant points. I did not find the format to be helpful in this regard. This format, combined with extremely large type headings and section spacing, resulted in a book that was fast to read but somewhat unsatisfying in the scope of its content.

This new series will compete with *Critical Care Clinics* published by Saunders since 1985. At the opposite end of the spectrum, the format of *Critical Care Clinics* uses an excessive amount of text per page (e.g., small type, more lines per inch, small margins, small subject headings). The July 1990 issue of the latter series on mechanical ventilation included 15 chapters and 317 pages of text. Although the *Critical Care Clinics* volume is smaller in actual size, it has more than twice as many words of text. The result is a book that is slower to read but discusses more topics in more detail. Newer modes of mechanical ventilation are comprehensively discussed in two chapters, allowing the inclusion of topics of interest to the anesthesiologist-intensivist such as airway management in the critically ill patient, the new generation of mechanical ventilators, complications associated with mechanical ventilation, and oxygen toxicity. Comparison of the corresponding chapters on weaning (both coauthored by Tobin) demonstrates a similar but more extensive approach in *Critical Care Clinics*.

The planned next four volumes of the *Contemporary Management in Critical Care* series are acid-base and electrolyte disorders, critical care toxicology, respiratory monitoring, and imaging and invasive radiology. Based on the initial book, this reviewer believes the series will be useful for the anesthesiologist with an interest in recent developments in critical care. The anesthesiologist extensively involved in critical care may prefer the slightly cheaper and more detailed *Critical Care Clinics*.

Ronald G. Pearl, MD, PhD
Stanford University School of Medicine
Stanford, California

Fiberoptics in Anesthesia

Volume 9, No. 1 of Anesthesiology Clinics of North America

James T. Roberts, ed. Philadelphia: W. B. Saunders, 1991, 198 pp, $32.00.

A decade ago few anesthesiologists were able to perform fiberoptic endoscopy. Today fiberoptic endoscopy is a vital skill in airway management. This is reflected by the increasing number of workshops in fiberoptic endoscopy and incorporation of formal training in anesthesia residencies. The guest editor has been actively involved in the management of difficult airways and in the leading edge in the growth of fiberoptics. This multiauthored book would be of interest to practicing anesthesiologists, anesthesia residents, and anyone else who wants to update his knowledge on fiberoptics in anesthesia.

This slim volume contains an extensive amount of valuable information in 14 chapters on fiberoptics organized into five basic areas. The first section details the historical development of fiberoptic endoscopy in medicine and how it evolved into anesthesia. The next section provides important information on the proper care and handling of the fiberoptic equipment, the physical properties, explaining

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how and why fiberoptics works, and finally the ancillary and adjunct equipment available to facilitate fiberoptic endoscopy. The third section, which is the largest section, appropriately is devoted to patient care. The anatomy of the airway is reviewed briefly, followed by a detailed description of the preparation of the adult and pediatric patient for fiberoptic endoscopy. This description includes the preoperative assessment, application of topical anesthesia, and placement of an endotracheal tube or double-lumen tube in the trachea with the aid of the fiberscope. To complete this section, a variety of anesthetic dilemmas involving the airway in general anesthesia practice are presented and discussed, highlighting the indication and contraindication for using the fiberscope. The fourth section presents findings on studies involving teaching and learning of fiberoptic endoscopy delineating "what it takes to apply a new psychomotor skill." The last section of the book describes the future applications of fiberoptics in anesthesia.

Some of the contributors are established authorities and nationally known physicians who developed some of the ancillary equipment in the field of fiberoptics, which gives credibility to this book. For the most part, the book can be read from beginning to end with logical sequence for the novice. It can also be read by more experienced individuals by selecting chapters of interest. In particular, several chapters alone make this an important investment for one's library. For example, the chapter on fiberoptic endobronchial intubation provides concise and extensive information on the anatomy of the tracheobronchial tree, the development of different double-lumen tubes, placement and confirmation by auscultation and fiberoptic endoscopy, complication of double-lumen tube placement, development of new tubes for thoracic surgery, and finally placement of endobronchial blockers. In addition, this chapter contains many organized tables and diagrams that contribute to the ease of reading.

As far as redundancy usually seen in a multiauthored book, this reviewer found only one concept that was duplicated. Unfortunately, the diagrams of the innervation of the airway are rudimentary and lack specific detail on the location of important nerves and blood supply of the airway, particularly of the nasal cavity. In addition, all the photographs are in black and white. These deficiencies are minor and overcome by the multiple references presented at the end of each chapter.

Within many of the chapters, not only is there good factual knowledge but pearls of wisdom are spread throughout the book. For the novice, the practical advice to "give the antisialagogue first," could only assist one's effort in having a more successful experience with the fiberscope. This book provides the necessary insight to increase one's level of expertise in fiberoptics in anesthesia.

Gail I. Randel, MD
Department of Anesthesiology
University of Michigan Medical Center
Ann Arbor, Michigan

The Pediatric Anesthesia Handbook

Charlotte Bell, Cindy W. Hughes, and Tae Hee Oh, eds.
St. Louis: Mosby Year Book, 1991, 626 pp, $34.95.

The Pediatric Anesthesia Handbook is the result of the efforts of 27 resident and staff anesthesiologists at the Yale University School of Medicine to produce a pediatric anesthesia equivalent to the well-known *Harriet Lane Handbook,* a pocket manual written by and for pediatric resident physicians. The selection and organization of topics is on a level comparable to or better than that of other currently available pediatric anesthesia handbooks.

Standard topics such as pediatric anatomy and physiology, equipment, and various disease states unique to children are covered. Also included are well-written chapters on transplant surgery, anesthesia in remote locations, pain management, airway surgery, and ophthalmologic surgery. In general, the chapters are well-referenced and current, with sources as recent as 1990 included. A fairly complete list of the numerous pediatric syndromes with their anesthetic implications is also included. A useful comprehensive drug list of commonly used anesthetic and nonanesthetic medications in pediatrics is provided.

With many multiauthored books there is a disparity in the quality of writing. This text is no exception. Typographical errors, annoying omissions, inaccuracies, and sloppy writing in a number of chapters detract from the overall quality of the text.

Some errors, such as the atropine dose of 10–20 mg/kg listed on the inner cover, are obvious enough to even the most novice practitioner that they would be discounted. Other oversights are more bothersome. The text and table format of the chapter on premedication is redundant, with several discrepancies in dosage range of medications listed. NPO guidelines are listed twice in the text, differ in their recommendation for ingestion of both solids and clear liquids, and do not reflect the recent liberalization of NPO guidelines for clear liquid intake. Formulas to estimate appropriate endotracheal tube length are mislabeled as formulas for estimating internal tube diameter. The age at which a surgical procedure is done or a physiologic change is completed is occasionally listed without an accompanying unit. It is unclear whether the author is talking about days, weeks, months, or years. It is erroneously stated that succinylcholine may precipitate hyperkalemia in the patient with a myelomeningocele; that enflurane and hypercarbia, rather than hypocarbia, can cause seizures; and that hyper- rather than hypophosphatemia is seen in primary hyperparathyroidism. Use of the superficial temporal artery for preductal arterial pressure monitoring is mentioned in the text, yet is not something used by most clinicians. The chapter on congenital heart disease contains several confusing statements and inaccuracies.

The chapter on malignant hyperthermia (MH) implies that all patients with suspected MH be treated as positive regardless of muscle biopsy results. Many MH experts would disagree. It is also stated that the MH muscle biopsy test is not standardized. There are presently standards promoted and enforced by the MH Registry. The muscle weakness seen with dantrolene is overemphasized. It is rarely a reason for ICU admission and "prolonged ventilation." There are a number of misspellings and incorrect indexing of words in the index. The present 6.5 × 8.5-in dimensions (including the ring binder) are not pocket-sized, making it difficult to carry in a lab coat.

The subspecialty of pediatric anesthesia has not escaped the recent explosive increase in medical literature, with almost a dozen subspecialty books presently available. One must question the need for yet another addition. A niche does, however, exist for a well-written pocket manual for the anesthesia resident. With elimination of inaccuracies, improved editing of several chapters, and downsizing of the book, this reasonably priced handbook can fill that niche.

Patrick K. Birmingham, MD
Department of Anesthesia
Children's Memorial Hospital
Chicago, Illinois

Improving Anesthesia Outcome

Volume 5, No. 2 of Problems in Anesthesia

John H. Eichhorn, ed. Philadelphia: J.B. Lippincott, 1991, 180 pp, $30.00 for single issue or $70.00 subscription for four issues.

When medical historians of the next century are summarizing the changes in anesthetic practice that occurred in the past decade, this monograph will surely be studied for insight. In a concise and very readable format the monograph details the convergence of technology and economic incentive that has led to standards in monitoring and improved care.

Although epidemiology does not lend itself to conventional scientific design, convincing arguments are set forth that there has been a marked change in anesthetic morbidity and mortality. The chapters on machine standards, pulse oximetry, and capnography are especially well written. The chapter on educational initiatives provides insightful reviews of some of the more controversial issues of human error and anesthetic practice while also examining the utility and efficacy of continuing medical education in anesthesia. The references are accurate and the index helpful for review. The only criticism this reviewer would venture, is that a more balanced presentation might have been achieved had leading dissenters such as Keats or Orkin been given the opportunity to delineate their views in the text directly rather than by citation.

This monograph will be of particular value in providing historical prospective and speculation to those who are leaders in anesthesia such as departmental chairmen and residency directors as well as officers of anesthesia organizations. With the approach of the sesquicentennial of the first demonstration of anesthesia, hard statistical answers to mortality trends may become available. In the interval, this text serves as an excellent guide to the improvements in care and outcome that have occurred.

Clifford M. Gevirtz, MD, MFH
Department of Anesthesia
Albert Einstein College of Medicine/
Montefiore Medical Center
Bronx, New York

Intraoperative Use of Echocardiography

Norbert P. deBruijn and Fiona M. Clements, eds.
Philadelphia: J. B. Lippincott, 1991, 225 pp, $49.95.

Intraoperative Use of Echocardiography is a multiauthored hardback monograph from the Society of Cardiovascular Anesthesiologists. The editors have compiled a series of chapters that cover the present knowledge, clinical application, and future directions of intraoperative echocardiography as it applies to the practicing anesthesiologist. The text covers a large amount of material in a compact and readable format. The monograph is not intended as a replacement for a more comprehensive text or as an instruction manual, but rather as a review of the more basic concepts and clinical applications of intraoperative echocardiography.

The monograph is well organized and well written and the reader will gain an understanding of the basic concepts of echocardiography and its clinical application in the operating room. Limitations include the absence or only brief discussion of the normal transesophageal echocardiographic examination, the standard views of the heart, the normal cardiac anatomy, and the echocardiographic assessment of intracardiac tumors, mural thrombi, aortic dissection, heart valve vegetations, and intracardiac abscesses. There is some redundancy between chapters, especially on the topic of physics and technology of Doppler. Quality of the two-dimensional images presented in the monograph are good but do not do justice to the instrumentation currently available, which can produce images with much better clarity and resolution. The graphs, drawings, and tables are excellent supplements to the text and significantly enhance the concepts that the authors are attempting to convey to the reader. Most chapters include a comprehensive list of primary references from peer-reviewed journals. However, the chapter on valvular dysfunction and repair, which is the most important application of intraoperative echocardiography, has the fewest references.

Overall, *Intraoperative Use of Echocardiography* is a useful text for the physician interested in the clinical application of intraoperative echocardiography. The text is useful for the individual who wants to become familiar with the terminology and images that are becoming more commonplace in the cardiac surgery arena. In addition, the monograph is a suitable beginning text for the reader interested in pursuing a more advanced understanding of this new and sophisticated technology. Drs. deBruijn and Clements should be applauded for their effort because a book of this nature has been long overdue.

Stuart J. Weiss, MD, PhD
Albert T. Cheung, MD
Joseph S. Savino, MD
Department of Anesthesia
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

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Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying

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FELLOWSHIP IN CRITICAL CARE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

Applications are solicited for a one year Critical Care Fellowship beginning in July 1992. Clinical training will include rotations on a combined surgery-anesthesia critical care team, a respiratory consultant service, a pediatric intensive care service, and a medical intensive care service. Research time will also be available. Please address correspondence with CV to:

Ralph T. Geer, M.D.
Department of Anesthesia
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104-4283

Cardiac Anesthesiologists

Cardiac and general anesthesiologists needed to join our team of 25 MDs, over 30 CRNAs and over 30 residents at Albany Medical College. Interest in teaching and research is highly desirable. The Albany Medical Center is a 660-bed, tertiary care facility with 20 newly renovated OR suites equipped with state-of-the-art instrumentation. Well established cardiac surgery program provides treatment for 1300 patients annually.

Benefits package includes generous leave time, health and dental plan, malpractice and life insurance. Interested applicants should send CV and 3 references to:

Philip D. Lumb, MB, BS
Professor and Chairman
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Dept of Anesthesiology
Mail Code A-131
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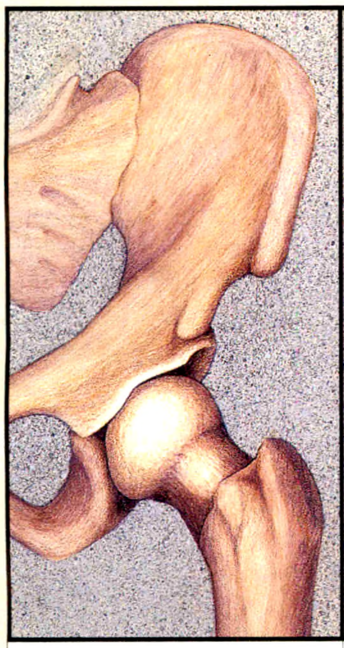
ALBANY MEDICAL CENTER

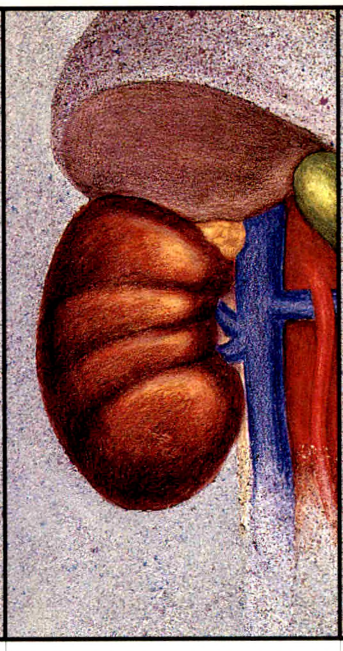
Tracrium®

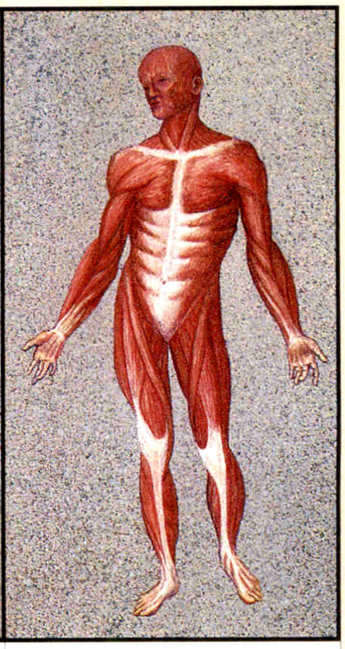
For many procedures

For many reasons

Cholecystectomy	**Biliary tract repair**
Common patient type Obese	**Common patient type** Both adults and children
Advantage of Tracrium No difference in recovery from neuromuscular blockade between normal and obese patients.[1]	**Advantage of Tracrium** Clinical response unaffected by hepatic function[2] or patient age.[3]







Total hip replacement	Renal surgery	Neurosurgery for trauma	Everyday procedures
Common patient type Elderly women and men	**Common patient type** Both adults and children	**Common patient type** Both adults and children	**Common patient type** Average
Advantage of Tracrium Recovery time unaffected by age.[3]	**Advantage of Tracrium** Recovery time unaffected by renal dysfunction.[2]	**Advantage of Tracrium** Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).[4,5]	**Advantage of Tracrium** The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

TRACRIUM® INJECTION

(atracurium besylate) 10 mg/mL

For predictable recovery

TR-Y03368

See brief summary of prescribing information on adjacent page.

TRACRIUM® INJECTION

(atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy: *Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8° C (36° to 46° F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25° C/77° F), use Tracrium Injection within 14 days even if rerefrigerated.

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1. Weinstein JA, Matteo RS, Ornstein E, Schwartz A, Goldstoff M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg.* 1988;67:1149-1153. **2.** Ward S, Neill EAM. Pharmacokinetics of atracurium in patients in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172. **3.** d'Hollander A, Luyckx C, Barvais L, DeVille A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology.* 1983;59:237-240. **4.** Ornstein E, Matteo RS, Silverberg PA, Schwartz AE, Young WL, Diaz J. Chronic phenytoin therapy and nondepolarizing muscular blockade. *Anesthesiology.* 1985;63:A331. Abstract. **5.** Ebrahim Z, Bulkey R, Roth S. Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg.* 1988;67:S55. Abstract.

Wellcome

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TR-Y03368

RESEARCH ASSOCIATE

Research Associate needed to conduct anesthetic, analgesic and other drug experiments. Require Masters Degree or equivalent in Biological Science, two years experience in anesthesia management of either human or animals and knowledges of anesthetics, analgesics, animal handling, blood sample processing; experience in intravenous, intramuscular and subcutaneous administration of drugs. Salary $20,000 dollar per year. Job Order No. 2819317

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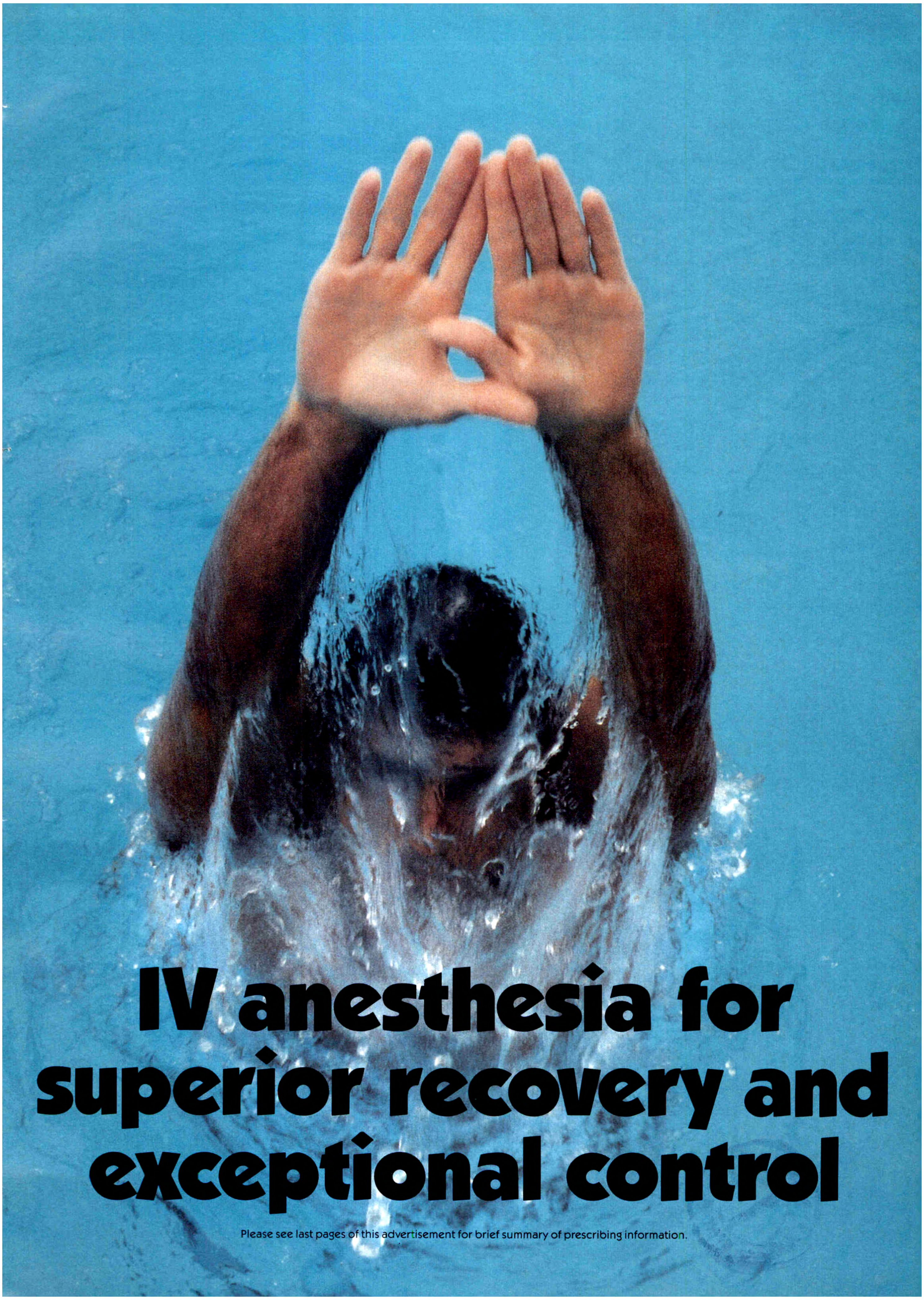
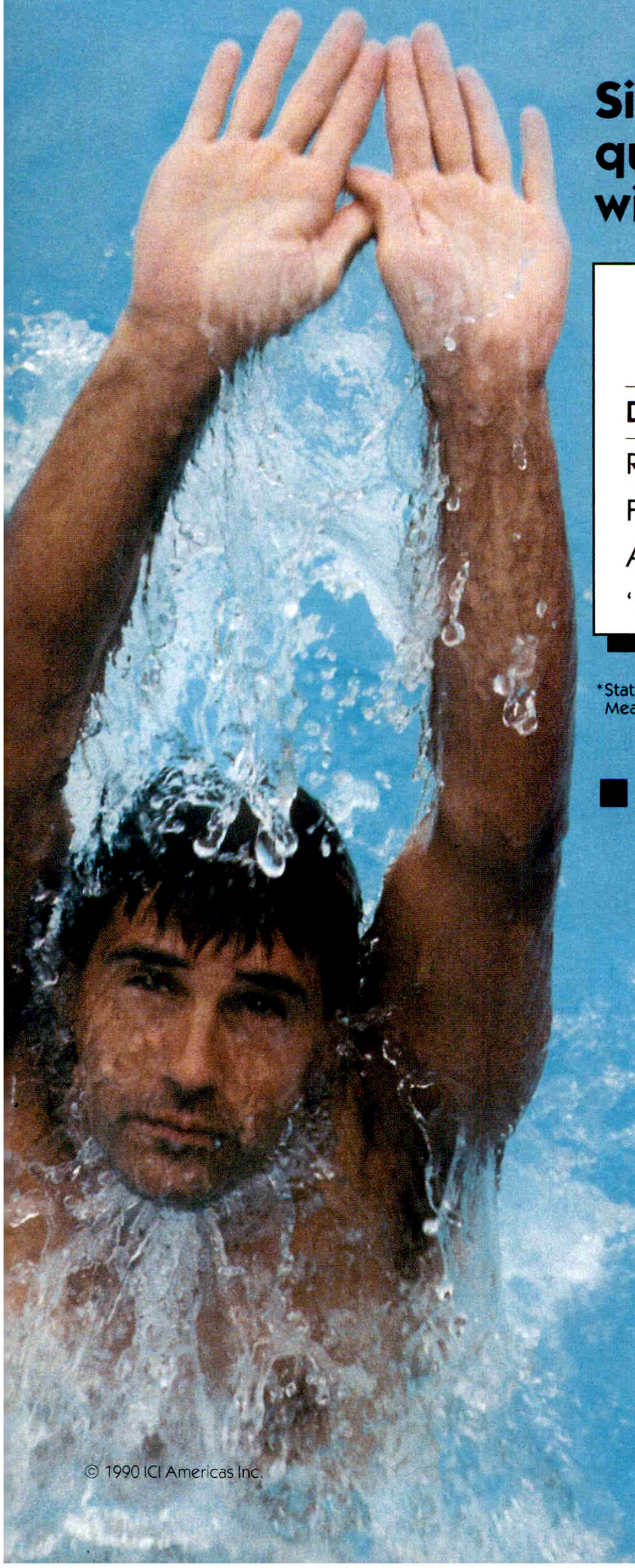

IV anesthesia for superior recovery and exceptional control

Please see last pages of this advertisement for brief summary of prescribing information.

Superior exceptional



Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

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recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®

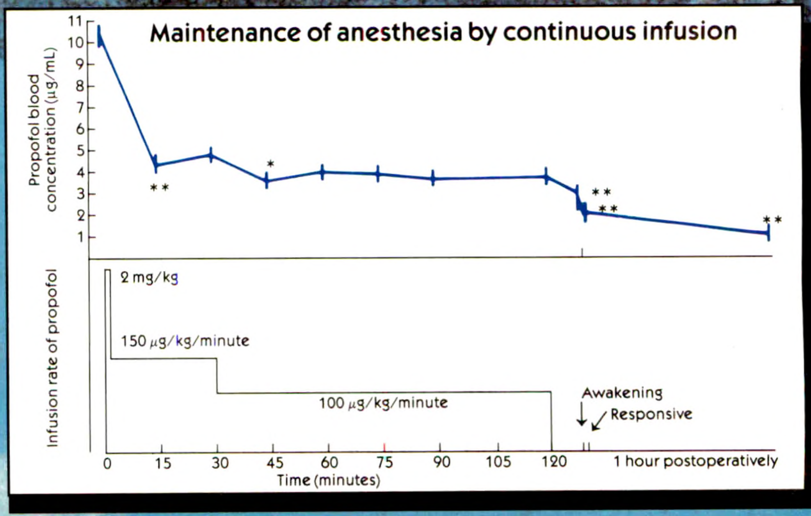
INJECTION

propofol

Superior exceptional

Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recovery, and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.
[†] Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®
INJECTION
propofol

For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: **1.** Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. **2.** Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. **3.** Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. **4.** Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. **5.** Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

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STUART PHARMACEUTICALS
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DIPRIVAN®

INJECTION
10 mg/mL
propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.) DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.) **CONTRAINDICATIONS:** When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components. **WARNINGS:** DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.** DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known. **Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.) PRECAUTIONS: General:** A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home. When DIPRIVAN Injection is administered to an epileptic patient, there may be a risk of convulsion during the recovery phase. Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae. Perioperative myoclonia, rarely including convulsions and opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear. DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli. **Information for Patients:** Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia. **Drug Interactions:** The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae,* in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. **Nursing Mothers:** DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. **Pediatric Use:** DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. **Neurosurgical Anesthesia:** Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures. **ADVERSE REACTIONS:** Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. **Incidence Greater than 1%—All events regardless of causality, derived from clinical trials. Body as a Whole:** Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement*, Headache, Dizziness, Twitching, Bucking/Jerking/ Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea**, Vomiting*, Abdominal Cramping. **Injection Site:** Burning/Stinging**, Pain**, Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing. Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater. **Incidence Less than 1%—Causal Relationship Probable** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*) **Body as a Whole:** Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.* **Incidence Less than 1%—Causal Relationship Unknown** (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.)* **Cardiovascular:** Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, *Myocardial ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine. **DRUG ABUSE AND DEPENDENCE:** None known. **OVERDOSAGE:** To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents. The intravenous LD_{50} values are 53 mg/kg in mice and 42 mg/kg in rats. **DOSAGE AND ADMINISTRATION: Induction:** Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.) Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction. **Maintenance:** Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections. When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates. **Continuous Infusion:** DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times. **Intermittent Bolus:** Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	**DOSAGE AND ADMINISTRATION**
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic, and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion**—titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration. **Dilution Prior to Administration:** When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.) **Administration Into a Running IV Catheter:** Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter: 5% Dextrose Injection, USP; Lactated Ringers Injection, USP; Lactated Ringers and 5% Dextrose Injection; 5% Dextrose and 0.45% Sodium Chloride Injection, USP; 5% Dextrose and 0.2% Sodium Chloride Injection, USP. **Handling Procedures:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. DIPRIVAN Injection must not be administered through a microbiological filter because this could restrict the flow of DIPRIVAN and/or cause the breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion. Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When using vials with volumetric infusion devices insert sterile vent spike through rubber stopper and immediately connect IV line. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection, reservoirs, IV lines or solutions containing DIPRIVAN Injection must be discarded at the end of the anesthetic procedure. Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness. *Aseptic Technique* for Handling DIPRIVAN Injection Ampules:* • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask and hair cover. • Disinfect neck surface of ampule using 70% isopropyl alcohol. Swab neck of ampule by wiping in one direction and let dry. • Protect fingers and hands by using sterile gauze when opening the ampule. • Withdraw DIPRIVAN Injection into a sterile syringe. • Immediately replace needle cap and discard ampule. • Label syringe with appropriate information, including date, time and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours—whichever occurs sooner. *Aseptic Technique* for Handling DIPRIVAN Injection Vials (and for Use With Volumetric Infusion Devices):* • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask and hair cover. • Remove metal cap from vial. • Disinfect rubber stopper of vial using 70% isopropyl alcohol. Wipe in one direction and let dry. • Insert sterile vent spike through rubber stopper and remove luer cap. • Connect a sterile syringe(s) to vent spike and withdraw entire contents; (Or when using volumetric infusion devices, aseptically connect IV line to vent spike). • Immediately cap syringe(s) with sterile closure(s) and discard vial and vent spike. • Label syringe(s) (or vial when using volumetric infusion devices) with appropriate information, including date, time and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours—whichever occurs sooner. *These techniques are not intended to preempt more stringent, established institutional guidelines for the aseptic handling and administration of sterile parenteral drug products. **HOW SUPPLIED:** DIPRIVAN Injection is available in ready to use 20 mL ampules and 50 mL infusion vials containing 10 mg/mL of propofol.

20 mL ampules (NDC 0038-0290-20) 50 mL infusion vials (NDC 0038-0290-50)

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

Rev D 02/91

Made in Sweden
Manufactured for:
STUART PHARMACEUTICALS A business unit of ICI Americas Inc., Wilmington, DE 19897 USA

Classified Advertising

FLORIDA
BC/BE anesthesiologist for expanding ambulatory group practice. Part time/full time with no nights, emergencies, OB, or weekends. Please reply to Box 621C/L.

621C/L

POSTDOCTORAL FELLOWSHIP
Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

674E/D

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

701G/F

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY
The Department of Anesthesiology at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in Cardiovascular Anesthesiology beginning July 1992. The fellowship is a 2-year, comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conferences, and teaching responsibilities are part of the fellowship experience. Interested individuals should contact Jorge Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico, 2211 Lomas Blvd. NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

730H/C

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology has an immediate opening for a Veterans Administration Chief of Service for Anesthesia at the New Mexico Regional Medical Facility (VA Hospital) in Albuquerque. Requirements include proven administrative, teaching, and leadership abilities, academic experience, and board certification. Appointment will be at the Associate Professor level. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

731H/C

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology has faculty positions beginning July 1992 for the following: (1) Obstetrical Anesthesia at the Assistant, Associate, or Full Professor levels; (2) Critical Care Medicine at the Assistant or Associate Professor level. It is expected that candidates for CCM positions will have or be eligible for subspecialty certification. Faculty responsibilities include provision of clinical care, teaching, and research. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

732H/C

THE UNIVERSITY OF NEW MEXICO
Department of Anesthesiology has faculty positions at the Instructor, Assistant Professor, and Associate Professor levels beginning July 1992. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

733H/C

PAIN MANAGEMENT FELLOWSHIP
Unique training opportunity for highly motivated, patient-oriented, anesthesiologist to participate in strong clinical pain management program. Emphasis on comprehensive evaluation and the use of neural blockade in the treatment of acute, chronic, and cancer pain. Training in interventional pain management techniques including implantable drug delivery systems and CT-guided neurodestructive procedures.

Applicant must possess strong interest in regional anesthesia and desire one-on-one patient contact. No OR or OB anesthesia responsibilities. Applicant MUST be BC/BE in anesthesia before beginning training. Fellowship period—1 year. Interested applicants should send CV to Pain Consortium of Greater Kansas City, 11111 Nall #202, Leawood, KS 66221.

714H/A

OHIO
ANESTHESIOLOGIST—METROHEALTH MEDICAL CENTER. Must be at least board

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CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

eligible. Equal Opportunity Affirmative Action Employer. Send curiculum vitae to Lee S. Shepard, MD, Director, Department of Anesthesiology, MetroHealth Medical Center, 3395 Scranton Road, Cleveland, OH 44109.

727H/A

ANESTHESIOLOGIST

Three-man anesthesia group affiliated with multispecialty group seeks fourth physician for burgeoning practice. Competitive compensation benefit package including incentives. For more information contact Physician Recruiter, 850 Ridge Lake Boulevard G02, Memphis, TN 38120; (901) 684-3423.

751I/B

BE/BC ANESTHESIOLOGIST

SW PA, 300-bed, modern community hospital to work with three MDs and CRNAs. Competitive starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to Box 753I/L.

753I/L

BLACK HILLS SOUTH DAKOTA

Single Hospital Regional Medical Center needs one or two anesthesiologists now. Care team practice with CRNAs. All specialties except cardiac. Low-stress practice. Wonderful setting. Clean air. Low crime. Details: Rapid City Anesthesia Services, P.C., P.O. Box 1560, Rapid City, SD 57709.

768J/L

DEPARTMENT OF ANESTHESIOLOGY

St. Louis University School of Medicine is seeking board-qualified or certified full-time faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, pain, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110-0250; telephone (314) 577-8750.

772J/C

MEDICAL DIRECTOR, PAIN MANAGEMENT CENTER UNIVERSITY OF NEBRASKA MEDICAL CENTER

Exciting opportunity for motivated, board certified/eligible anesthesiologist for faculty position, as the Medical Director of an established Pain Management Center. The Pain Management Center has an active and growing acute and chronic pain management program. Position involves direct clinical work with acute and chronic pain patients, supervision and teaching of residents and students, as well as opportunities for basic and/or clinical research and program development. Prerequisites include experience in acute and chronic pain medicine. Responsibilities include directorship of a multidisciplinary outpatient pain control center.

Position at the Assistant or Associate Professor level with competitive salary commensurate with experience and qualifications. Excellent and complete compensation package including bonus potential. Full academic participation, didactic and clinical teaching.

The University of Nebraska Medical Center is designated a Level I trauma center and has an active liver and bone marrow transplant program among other strong clinical programs. The Leon S. McGoogan Library of Medicine is one of the seven designated Midcontinental Regional Medical Libraries in the U.S.

Send curriculum vitae and two letters of reference by December 31, 1991 to Dennis F. Landers, MD, PhD, Chairman, Department of Anesthesiology, University of Nebraska Medical Center, 600 South 42nd St, Omaha, NE 68198-4455. The University of Nebraska is an Affirmative Action/Equal Opportunity Employer.

773J/L

DIRECTOR, PAIN MANAGEMENT SERVICE

The Department of Anesthesiology at the Oregon Health Sciences University is recruiting for a Director of our Pain Management Service. The Service encompasses management of acute and chronic pain, training of medical students, residents, and fellows, and research. The Service provides a multidisciplinary approach to pain control and has vigorous clinical psychology and neuroimplant components. Excellent interdisciplinary relationships exist with Neurosurgery, Orthopedics, and Surgical Oncology. Board eligibility in anesthesiology or equivalent certification plus training and/or experience in pain management are required. Research experience and evidence of productivity are desired. Academic rank for successful candidate will be determined by qualifications. Candidate must be eligible for Oregon medical license.

Please send curriculum vitae and names of three references to Wendell C. Stevens, MD, Department of Anesthesiology, OHSU, 3181 SW Sam Jackson Park Road, Portland, OR 97201. The Oregon Health Sciences University is an Equal Opportunity/Affirmative Action Employer.

774J/L

ASSOCIATE IN PAIN MANAGEMENT OREGON HEALTH SCIENCES UNIVERSITY SCHOOL OF MEDICINE

The Department of Anesthesiology at the Oregon Health Sciences University School of Medicine is recruiting for a full-time faculty member at the Assistant Professor level. The successful recruit will have an academic appointment in the School of Medicine and will have teaching and research responsibilities in the Pain Management Center of our University Hospital. Candidates should have specific training (at least 3 months) in pain management and related research and should have experience in a multidisciplinary pain management center. Candidates should have an aptitude for research, demonstrated by primary authorship of peer-reviewed publications in the field of pain management and/or regional anesthesia. Ability to interact with basic and clinical scientists should be shown. Candidate should be certified by the American Board of Anesthesiology and have an Oregon medical license. Interested candidates should send their curriculum vitae and the names of three references to Wendell C. Stevens, MD, Department of Anesthesiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201. The Oregon Health Sciences University is an Equal Opportunity/Affirmative Action Employer.

775J/L

ARKANSAS, LITTLE ROCK

Group of seven MDs and 10 CRNAs searching for one or two BC/BE anesthesiologists. All types of anesthesia with some CRNA supervision. Opportunities available in pain management. 341-Bed hospital. Well-established group with equally shared call, vacation, and benefits. Beautiful rolling hills and abundant outdoor recreational activities in the area. Send CV to Garry Jones, MD, Capitol Anesthesia Group, St 606, 500 South University, Little Rock, AR 72205.

777J/A

PEDIATRIC ANESTHESIOLOGY FACULTY

Section of Pediatric Anesthesiology at the University of Michigan Medical School is seeking an additional faculty member. The Section provides anesthesia for a surgical caseload of 6000 cases/year, 50% of which are outpatients. All pediatric surgical subspecialties are represented, with an active pediatric cardiac surgery program of over 500 cases/year. An expanding pediatric pain program is currently being developed. Candidates should be BE/BC with a fellowship in pediatric anesthesiology. Appointments can be from the Lecturer to the Professor level in either the clinical or academic track, depending on qualifications and experience. Resources are available for faculty to participate in clinical and laboratory research. Interested candidates should apply to Niall Wilton, MD, Chief, Section of Pediatric Anesthesiology, C-4139, Med Inn Bridge, Box 0800, University of Michigan Medical Center, Ann Arbor, MI 48109-0800 (FAX 313-936-9091). The University of

Michigan is a nondiscriminatory, Affirmative Action/Equal Opportunity Employer.

778J/I

WASHINGTON, D.C.

Positions available immediately and during the next year for full-time BE/BC anesthesiologists to join a growing MD/CRNA practice. Large ambulatory and challenging tertiary care caseload including all specialties except pediatrics at university-affiliated hospital. Reasonable call schedule with competitive compensation package and partnership after 1 year. Send or fax CV to Barney S.H. Feinstein, MD, Chairman, Department of Anesthesia, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010; Fax number (202) 877-5564 or call collect (202) 877-7500.

721H/A

AVAILABLE IMMEDIATELY

In the Greater Cleveland Area a position for an MD anesthesiologist with Fellowship and/or Pain Management. Department has a very rapidly growing Pain Management Center, wide variety of blocks and invasive procedures performed. Active ongoing research. Must be able to contribute significantly to the growth in this area, in addition to operating room duties. No OB or hearts. Excellent compensation and benefits leading to early partnership. If interested apply to Box 734HIKL with current CV.

734HIKL

ILLINOIS

Large, well-established, single-specialty group of anesthesiologists seeks additional BC/BE anesthesiologists. Challenging opportunity for those interested in a broad-based practice. All surgical subspecialties represented with coverage at three hospitals and two day-surgery facilities. Excellent benefits with early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 64614.

785K/F

LOUISIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT

Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center-Shreveport, 1501 Kings Highway, Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.

788K/D

The Pain Consortium of Greater Kansas City is seeking a BC/BE anesthesiologist to serve as Associate Clinical Director. An excellent career opportunity for a highly motivated individual who is interested in practicing full-time pain management with an innovative and busy pain management team. Excellent people skills and a desire for one-on-one patient contact is necessary. Above-average general medical knowledge and ability in the use of neural blockade in the treatment of pain is a must. Willingness to participate in active clinical research and our fellowship training program is desirable. If you are a hard-working and quality-minded team player—this may be the job you've been looking for. Send your CV and three letters of recommendation to Steven D. Waldman, MD, Director, Pain Consortium of Greater Kansas City, 11111 Nall #202, Leawood, KS 66211.

790K/A

NORTHERN NEW ENGLAND

Staff anesthesiologist, BC/BE for 194-bed VA Medical Center, fully integrated academic anesthesiology department of the Dartmouth-Hitchcock Medical Center and Dartmouth Medical School. Active teaching hospitals. Academic appointments and salary commensurate with experience. Part-time position a possibility. Good schools, cultural offerings, beautiful country environment, good skiing, excellent book store. 2.5 hours from Boston, Massachusetts; 1.5 hours from Burlington, Vermont. For further information, call Andrew Gettinger, MD, Chairman VA Anesthesia Search Committee, or D. David Glass, MD, Chairman, Department of Anesthesiology, (603)646-5922 (FAX: (603) 646-8980). Or send CV to above at Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756. EOE/MF.

792K/A

PENNSYLVANIA

Faculty position available at Wills Eye Hospital. Board certification or presently in the examination system required. The candidates should have interest and expertise in pediatric and neonatal anesthesia. The successful candidate will have a full-time faculty position in the Department of Anesthesiology of Thomas Jefferson University. This is an excellent opportunity for teaching and research at one of the most prestigious ophthalmologic hospitals in the country. Thomas Jefferson University is an Affirmative Action/Equal Opportunity Employer. Send CV and references to Joseph L. Seltzer, MD, Professor and Chairman, Department of Anesthesiology, Thomas Jefferson University, 111 South 11th Street, Suite 6460 Gibbon, Philadelphia, PA 19107.

794K/A

ANESTHESIA CRITICAL CARE FELLOWSHIP: NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

Twelve-month ACGME-accredited Critical Care Fellowship position available for anesthesiology CA-4 (PGY V) candidates beginning July 1992 or January 1993. Clinical experience includes all aspects of critical care medicine in medical, neurosurgical, pediatric, surgical, and spinal cord ICUs. This fully accredited Critical Care Training Program has been functioning for over 10 years and is supervised by three full-time anesthesiology intensivists. Research opportunities available for those interested. Send inquiries and application request to Barry A. Shapiro, MD, Section of Respiratory and Critical Care Medicine, Department of Anesthesia, Northwestern University Medical School, 250 East Superior Street, Suite 678, Chicago, IL 60611.

798KL

ANESTHESIOLOGIST

Board certified/eligible to join expanding small group practice. Experienced in all anesthesia techniques including epidural block and pain management. No open heart or neurosurgery. Good opportunity for growth. Please send CV to Mount Vernon Anesthesia Associates, Box 391, Mount Vernon, OH 43050.

799K/A

OHIO

Anesthesiologist to join a professional corporation of 11 anesthesiologists and 40 CRNAs in a progressive, 500-bed hospital. Salaried position for day shift. No night call or holidays. Excellent financial compensation. Please reply with CV to Michael J. Hovan, MD, PhD, Chairman, Department of Anesthesia, Akron City Hosptial, 525 East Market Street, Akron, OH 44309.

800KL

Anesthesiologist to join group consisting of seven anesthesiologists and two CRNAs. Must be board eligible or board certified. Established PC with many fringe benefits in effect. Send CV to Associated Anesthesiologists of Saginaw, PC, 3121 Davenport, Saginaw, MI 48602 or call (517) 791-2150.

801KL

PAIN MANAGEMENT CENTER CODIRECTOR

The Medical College of Wisconsin is looking for a faculty member who is experienced in chronic and acute pain management to codirect a busy multidisciplinary pain management center. The pain center is located in a new 3500 sq ft clinic area and has full-time psychology, physical therapy, and nursing staff as well as five anesthesiology faculty, three anesthesiology residents, and one to two fellows. Treatment programs include spinal stimulation, chronic spinal opiate administration, and a full range of anesthesia-related modalities. Acute pain services are undergoing expansion. There are extensive opportunities for clinical and basic science research. If interested, call or write to Stephen E. Abram, MD, Department of Anesthesiology, Medical College of Wisconsin, 8700 West Wisconsin Avenue, Milwaukee, WI 53226. (414) 257-6259. Equal Opportunity/Affirmative Action Employer M/F/H.

803K/A

ARKANSAS
Pediatric Anesthesia Fellowship to begin July 1, 1992. Broad-based training in pediatric anesthesia includes experience in cardiac, pain management, and critical care. Active research program. Prefer applicants who have completed CA-3 level in approved residency program. Must be eligible for Arkansas licensure. Send curriculum vitae to Raeford E. Brown, Jr., MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An Equal Opportunity Employer.

806K/A

INDIANAPOLIS, INDIANA
Excellent public schools, universities, pro sports, full complement of fine arts, zoo, affordable housing, very stable economy, low crime, and excellent medical climate. Anesthesiologist needed for obstetrics at 1100-bed hospital. Possible Directorship. Excellent financial package. Interviewing and relocation expenses reimbursed. Send CV or call Neal Steinhoff, Jackson and Coker, Inc., 115 Perimeter Center Place, Suite 380 11370, Atlanta, GA 30346; telephone: 1-800-544-1987.

807LA

OHIO
A position is available for a mature clinically oriented anesthesiologist to become the Director of Operating Room Anesthesia Services at University Hospital. This position includes an appointment at the Associate Professor or Professor level in the Department of Anesthesia of the University of Cincinnati. Contact and send CV to Theodore W. Striker, MD, Department of Anesthesia, University of Cincinnati College of Medicine, Cincinnati, OH 45267-0531.

808L

ANESTHESIOLOGIST
Progressive, young, and expanding MD/CRNA group in suburban Kansas City, Missouri hospital is seeking BE/BC associate. Pain fellowship and/or interest in pain management desirable but not mandatory. Send CV to Don Adamson, PO Box 10370, Kansas City, MO 64111.

809L

ANESTHESIOLOGIST
Carle Clinic Association is seeking a BC/BE anesthesiologist, with advanced training in CV anesthesia, to join a 218-physician multispecialty group practice located in central Illinois. The Anesthesia Department is comprised of 9 anesthesiologists and 22 CRNAs providing services for cardiovascular surgery and neurosurgery as well as most other surgical procedures. Adjacent Carle Foundation Hospital is a 288-bed hospital and is designated as a level 1 Trauma Center. Competitive salary with bonus eligibility after the first year. Extensive fringe benefits include liability coverage; outstanding retirement package; health, life, and disability insurance; and excellent vacation and meeting time. Write including CV to Robert C. Parker, Jr., MD, Medical Director, Carle Clinic Association, 602 West University, Urbana, IL 61801; (217) 383-3399, Fax (217) 383-3163.

810L/B

YALE UNIVERSITY SCHOOL OF MEDICINE: DEPARTMENT OF ANESTHESIOLOGY
From time to time, faculty positions are available for both clinical anesthesiologists and research staff. These appointments are for immediate and future placement. Please respond prior to December 31, 1991 by sending your CV to Paul G. Barash, MD, Chairman, Department of Anesthesiology, Yale University School of Medicine, PO Box 3333, New Haven, CT 06510. Yale is an Affirmative Action Employer and provides equal opportunities for employment to all applicants.

811L

CENTER FOR PAIN MANAGEMENT, YALE UNIVERSITY
The Center for Pain Management, Department of Anesthesiology, Yale University School of Medicine is seeking a motivated attending anesthesiologist to assume an active role at the rank of Assistant Professor in the clinical care of acute and chronic pain patients as well as the teaching of medical students, residents, and fellows. There are ample opportunities for research at clinical as well as basic science levels. Candidates must be board eligible in anesthesiology and have completed a fellowship in pain management. Each candidate should also possess a strong interest in regional anesthesia as well as desire for one-on-one patient contact. Please send letters of inquiry by March 1, 1991 to Lloyd Saberski, MD, Medical Director, Center for Pain Management, Yale University, 333 Cedar Street, PO Box 3333, New Haven, CT 06510. Yale University is an Affirmative Action Employer.

812L

FLORIDA
Academic anesthesiologist. Two Assistant Professor positions available for board-certified or board-eligible anesthesiologists. Specialty training or experience in obstetrical anesthesia or pain management preferred. Positions available March 2, 1992 or later. Application deadline is January 2, 1992. Send request for interview and CV to Robert E. Redfern, MD, Search Committee Chairman, Department of Anesthesiology, University Medical Center, 655 West 8th Street, Jacksonville, FL 32209. Equal Employment Opportunity/Affirmative Action Employer.

813L

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY
The Department of Anesthesiology of the Medical College of Wisconsin is accepting applications for a 12-month fellowship in pediatric anesthesiology beginning July 1, 1992 (all candidates should have completed the CA-3 year). Experience and training will include all aspects of pediatric anesthesiology including cardiac anesthesia and pain management. Opportunity is also provided for clinical research and critical care experience. Inquiries, CV, and references should be sent to Stephen P. Pontus, MD, Section of Pediatric Anesthesiology, Children's Hospital of Wisconsin, PO Box 1997, MS 735, Milwaukee, WI 53201. Equal Opportunity/Affirmative Action Employer M/F/H.

814L/B

CA-1 POSITIONS IN ANESTHESIOLOGY
The Department of Anesthesiology at the Medical College of Pennsylvania, Allegheny Campus, Allegheny General Hospital, Pittsburgh, Pennsylvania, is accepting applications for CA-1 positions in Anesthesia for the 1992–1993 academic year. Send CV with letter to Allegheny General Hospital, Division of Anesthesiology, 320 East North Avenue, Pittsburgh, PA 15212.

815L/B

RESEARCH ASSOCIATE
Research Associate needed to conduct anesthetic, analgesic, and other drug experiments. Require Masters degree or equivalent in biological science, 2 years' experience in anesthesia management of either humans or animals, and knowledge of anesthetics, analgesics, animal handling, and blood sample processing; experience in intravenous, intramuscular, and subcutaneous administration of drugs. Salary $20,000 per year. Job Order No. 2819317. Contact Utah Job Service, 5735 South Redwood Road, PO Box 11750, Salt Lake City, UT 84147-0750. Employer is an EOE/AA Employer.

816L

CARDIOTHORACIC ANESTHESIOLOGIST-SOUTHEAST

An immediate need exists for a CV anesthesiologist to join one other in private practice. This physician works with a progressive 600+ bed teaching hospital and major referral center with three active cardiovascular surgeons doing over 600 open-heart cases per year. Candidate should be a BE/BC anesthesiologist with fellowship training in cardiothoracic anesthesia or extensive CV experience preferred. Contact Mary Wynkoop, Tyler and Company, 9040 Rosewell Road, Atlanta, GA 30350. Fax CV to (404) 641-6414, or call (800) 333-3910 or (404) 641-6409.

817L

CHIEF OF CARDIAC ANESTHESIOLOGY

Position available for a highly motivated board-certified anesthesiologist. Requirements include at least 4 years of postgraduate training, proven administrative, teaching, and leadership abilities, extensive adult and pediatric (<2 years of age) cardiac experience, as well as significant research experience. Please send letter and curriculum vitae to James E. Cottrell, MD, Professor and Chairman, Department of Anesthesia, SUNY, Health Science Center at Brooklyn, Box 6, 450 Clarkson Avenue, Brooklyn, NY 11203. SUNY/HSCB is an Affirmative Action/Equal Opportunity Employer.

818L

MICHIGAN

Two positions available for fee-for-service BC/BE anesthesiologists at 174-bed Catholic hospital. Four-member department will share call and 4000 annual cases. Little OB, no OH or neuro. Located 2 hours north of Grand Rapids, this congenial lakeside community of 26K offers an incredible range of outdoor recreation. Contact Therese O'Brien, Tyler & Company, 9040 Roswell Road, Suite 550, Atlanta, GA 30350. Phone: (800) 333-3911, Fax: (404) 641-6414.

819L

ANESTHESIOLOGY RESIDENCY OPPORTUNITY

The Department of Anesthesiology at the University of New Mexico School of Medicine has openings at the CA-2 and CA-3 levels. Rotations are available in cardiovascular, pediatric, obstetric, neuro, and pain (acute, chronic, and cancer) anesthesiology. Interested individuals should contact Jorge Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico, 2211 Lomas Boulevard NE, Albuquerque, NM 87106, (505) 272-2728. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

820L/B

TWO PEDIATRIC ANESTHESIOLOGISTS

Virginia Coast—needed to join MD/CRNA staff of university-affiliated children's hospital serving a diverse regional population. Fellowship or experience in pediatric anesthesia and board certification or eligibility required. Full spectrum of surgery. Responsibilities include clinical anesthesia and resident/CRNA education and supervision. Superb location on southeastern Virginia coast within easy access to beaches, mountains, and Washington, D.C. Salary commensurate with training and experience, complemented by an excellent benefit package. For more information contact James Mayhew, MD, Pediatric Anesthesiology, Room 315, Children's Hospital of The King's Daughters, 800 West Olney Road, Norfolk, VA 23507. AA/EOE.

821L/E

ANESTHESIOLOGIST/CRNA

Sinai Hospital, an acute care teaching hospital, in northwestern Detroit seeks a qualified anesthesiologist who is board certified or in the examination process. Sinai Hospital will also accept CRNA candidates. Salary will be commensurate with experience. The anesthesiologist candidate will be expected to participate actively in both undergraduate and resident education. Send CV to Mark McNash, Administrative Director, Sinai Hospital, 6767 West Outer Drive, Detroit, MI 48235. An Equal Opportunity Employer.

822LA

ISLAND LIVING—UNIVERSITY PRACTICE

Texas' first Medical School is located in a historic, resort community on the Gulf Coast, 45 minutes from Houston activities. Nationally recognized for its clinical excellence and outstanding residency program, The University of Texas Medical Branch, Department of Anesthesiology is seeking aggressive, talented clinician-teachers and clinician-investigators at all levels. Generalists and specialists are appreciated for the quality of their contributions. Time and support are available for investigations and career advancement. Generated income generously complements state salary and benefits. Send CV and references to Dr. Harry K. Wallfisch, UTMB, Department of Anesthesiology, E91, Galveston, TX 77550. UTMB is an Equal Opportunity/Affirmative Action Employer M/F/H/V. UTMB hires only individuals authorized to work in the United States.

823L

ANESTHESIOLOGIST

The Anesthesia Service, Veterans Affairs Medical Center, University Drive, Pittsburgh, Pennsylvania, is seeking candidates at the Assistant or Associate Professor level for teaching and clinical responsibilities at a referral center that includes cardiac surgery and liver transplantation. Candidates must have formal research training and experience. They must have training in liver transplantation. Responsibilities will include resident and medical student education and active research. Send CV and three references to Richard J. Bjerke, MD, Chief, Anesthesia Service, VAMC, University Drive, Pittsburgh, PA 15240. EOE.

824L

Immediate positions available for part-time anesthesiologists, Monday through Friday, 7:00 AM to 4:00 PM (no call), to join a group of 18 anesthesiologists and 8 CRNAs in northwestern Indiana, 30 minutes from downtown Chicago. Send curriculum vitae to Box 825L/C.

825L/C

ALABAMA—ANESTHESIOLOGIST FOR VA HOSPITAL

Faculty position for clinical BC/BE anesthesiologist at the Veteran's Administration Hospital with faculty appointment at The University of Alabama at Birmingham, Department of Anesthesiology. Opportunities to do clinical and basic research. Desire to participate in teaching residents necessary. Located in downtown Birmingham and adjacent to the UAB Medical Center. Birmingham was rated "America's most livable city" by U.S. Conference of Mayors, June 1989, and rated by *Newsweek*, February 1989, as "one of the nation's top 10 hot cities." Please contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205) 934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

826L/B

ALABAMA—CHIEF ANESTHESIOLOGIST FOR VA HOSPITAL

Faculty position for clinical BC Chief Anesthesiologist at the Veteran's Administration Hospital with faculty appointment at The University of Alabama at Birmingham, Department of Anesthesiology. Desire to participate in teaching residents and in clinical or basic research, as well as to guide junior faculty in their research endeavors is necessary. Located in downtown Birmingham and adjacent to the UAB Medical Center. Birmingham was rated "America's most livable city" by U.S. Conference of Mayors, June 1989, and rated by *Newsweek*, February 1989, as "one of the nation's top 10 hot cities." Please contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama of Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205) 934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

827L/B

ANESTHESIOLOGIST
Carl Vinson VA Medical Center in Dublin, Georgia is actively recruiting for a board certified/board eligible anesthesiologist in this rapidly expanding facility. An increasing number of outpatient clinic visits, sharing agreement with other health care providers, a nine-million dollar clinical addition coming up shortly, are only a few of the exciting developments in this institution. Safe, high-quality schools, a low cost of living, warm climate, low crime rate, excellent recreational opportunities, and proximity to most major cities of Georgia make Dublin a highly desirable place to live.

English language proficiency is required for all direct patient care positions. Carl Vinson VA Medical Center is a smoke-free facility with designated smoking shelters. All interested candidates are strongly encouraged to send their curriculum vitate to K. R. Varma, MD, Chief, Surgical Service; Telephone (912) 277-2746. An Equal Opportunity Employer

829LA

MICHIGAN
Recently trained BE/BC anesthesiologist wanted to join active practice in busy 127-bed hospital. Wide variety of cases. Very friendly atmosphere. Recreationally oriented Lake Michigan community. Competitive salary package with future partnership will wait for right person. Inquiries to: Jeffrey Kommit, DO, P.O. Box 517, Grand Haven, MI 49417.

830L/C

MAINE - NEEDED - ANESTHESIOLOGIST
To join 5-anesthesiologists, 10-CRNA group doing wide range of surgeries at two community hospitals. No open heart. Picturesque central Maine location near lakes, mountains, and ocean. Referral area of 75,000+. Competitive compensation package. Contact Jill Gilbert at (207) 872-1136 or send CV to Waterville Anesthesia Associates, 44 Main Street, Waterville, ME 04901.

828L/C

A WEEKEND OF MOCK ORAL EXAMS.
Mock orals, not lectures. We are the original course in this format. 20 hours category I CME credit, two board-certified instructors, 12 students maximum Tampa, January 17–19 and February 14–16; Dallas, March 6–8. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480 or (813) 394-8780.

781K/A

DON'T FAIL. PREPARE EARLY.
Unique approach for passing the written ITE/boards. Study questions, memory enhancement, guessing techniques, much more. 1991-92 edition. Call MEDTEXT 1-800-695-6301 24 hours.

757I/C

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Daniel & Yeager is the only name you need for locum tenens. Anesthesia is our exclusive specialty, so you are assured of our undivided attention. Earn a premium income while eliminating administrative headaches and malpractice premiums, we cover it all. Call 1-800-955-1919 or write to PO Box 2065, Huntsville, AL 35804-2065.

629C/B

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS
The unique feature of these programs is the maximum class size of four students. Preparation for the written and oral exams are given separately in 3-day blocks in San Francisco and New York. FOR THE WRITTENS, techniques are taught for dealing with the multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, the guided case discussions are stressed. Home study programs are provided. CALL (415) 321-1117.

763I/B

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598B/L

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755I/B

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
66th CONGRESS — March 13–17, 1992
San Francisco Hilton • San Francisco, California

SCIENTIFIC PROGRAM

T.H. Seldon Distinguished Lecture, Sunday, March 15, 11 AM,
"Anesthesiology—Pace Setter or Follower?"
Jerome H. Modell, MD, Senior Associate Dean for Clinical Affairs,
University of Florida College of Medicine, Gainesville, Florida

REVIEW COURSE LECTURES:

PO Bridenbaugh, MD	—Post-op Pain Relief, Does the Technique Matter?
L Broadman, MD	—Regional Anesthesia in Children
RA Caplan, MD	—Anesthetic Malpractice—What It Is and What It Isn't
BF Cullen, MD	—Anesthetic Management for the Trauma Patient
JC Drummond, MD	—Cerebral Ischemia: State of the Art Management
EI Eger II, MD	—The New Inhaled Anesthetics—Sevoflurane and Desflurane
M Finster, MD	—Management of the High Risk Obstetrical Patient
S Gelman, MD	—Preservation of Renal Function During Surgery
GS Hartman, MD	—Anesthesia for the Thoracic Surgical Patient
PR Hickey, MD	—The Patient With Congenital Heart Disease for Non-cardiac Surgery
PA Kapur, MD	—Controversies in Outpatient Anesthesia
RD Miller, MD	—AIDS and the Anesthesiologist
M Mulroy, MD	—Complications of Regional Anesthesia
WS Nimmo, MD	—Practical Pharmacokinetics for the Clinician
RJ Palahniuk, MD	—Controversies in Obstetric Anesthesia
RG Pearl, MD	—New Techniques in the Management of Shock
DS Prough, MD	—Cardiopulmonary Bypass and the Brain
JG Reves, MD	—Rationale and Methods of Infusion Anesthesia
JJ Savarese, MD	—New, Newer, Newest, and Imaginary Muscle Relaxants
B Spiess, MD	—The Coagulation System—Intraoperative Measurement and Management
T Stanley, MD	—Anesthetic Delivery Systems in the 1990s
RK Stoelting, MD	—Anesthesia for the Patient With Endocrine Disease
JH Tinker, MD	—Quality Assurance—A Lesson From the Japanese
KK Tremper, MD	—Oximetry, Capnography, Other Non-invasive Wizardry
H Van Aken, MD	—Anesthetic Management of the Patient With Head Injury
D Warltier, MD	—Cardiac Physiology for the Clinician

PANELS

Does the Choice of Anesthetic Technique Really Matter?—KJ Tuman, MD, Saturday, March 14

Clinical Cases From the Real World—JL Waller, MD—Monday, March 16

Critical Incidents in Anesthesia: Analysis and Prevention—DM Gaba, MD, Tuesday, March 17

TUTORIALS

Informative Tutorial Sessions will be offered in a small schoolroom setting on the following topics:

Vasoactive Drugs—NW Lawson, MD
Regional Anesthesia—AR Brown, MD
Introduction to Statistics—NL Pace, MD
Patient With Non-coronary Heart Disease—SJ Thomas, MD
Transesophageal Echocardiography—MK Cahalan, MD
Fiberoptic Bronchoscopy—JT Roberts, MD
How to Publish—DR Bevan, MB
ASA Task Force on Guidelines (Open forum on guidelines for difficult airway management. All interested individuals are invited to attend. Robert A. Caplan, MD, ASA Task Force Chairman)

LUNCHEONS

Cardiopulmonary Bypass in the 90s—Saturday, March 14
Pain Management—Who to, How to, Payment for—Sunday, March 15
Legislative/Economic Update—Monday, March 16

CLINICAL AND RESEARCH PRESENTATIONS

More than 350 clinical and research papers will be presented in concurrent oral, poster, and poster discussion sessions.
CME CREDIT—27 hours in Category 1

MEETING REGISTRATION, HOTEL RESERVATION, SCIENTIFIC MEETING INFORMATION: Will be mailed in December to all IARS members. (IARS members outside of North America who plan to attend the meeting will receive this material by airmail upon request.) Non-IARS members should request information from the **IARS OFFICE:** Suite 140, 2 Summit Park Drive, Cleveland, OH 44131. Tel: (216) 642-1124.

MEETING SCHEDULE: **Registration:** Friday, March 13, 1–6 PM
Scientific Program: Saturday–Tuesday, March 17
Exhibits: Saturday–Monday, March 16

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

IARS 66th CONGRESS

Friday, March 13 through Tuesday, March 17, 1992

T. H. Seldon Distinguished Lecture
Jerome H. Modell, M.D.
"Anesthesiology: Pacesetter or Follower?"

SAN FRANCISCO HILTON • HILTON SQUARE

Program Highlights: 26 Review Course Lectures; Panels on Anesthetic Technique, Clinical Cases from the Real World, and Human Performance Issues; Tutorials on Vasoactive Drugs, Regional Anesthesia, Statistics, Transesophageal Echocardiography, Fiberoptic Bronchoscopy, Publishing, and Patients with Non-Coronary Heart Disease; Luncheons have been scheduled to discuss Cardiopulmonary Bypass, Pain Management and current Legislative/Economic issues. Over 350 clinical and research papers will be presented in oral, poster and poster discussion sessions. Detailed program information will be sent to all IARS members in December, 1991.

International Anesthesia Research Society
2 Summit Park Drive, Suite 140
Cleveland, Ohio 44131, USA
Telephone: (216) 642-1124

Please send ______ Congress Information
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Name

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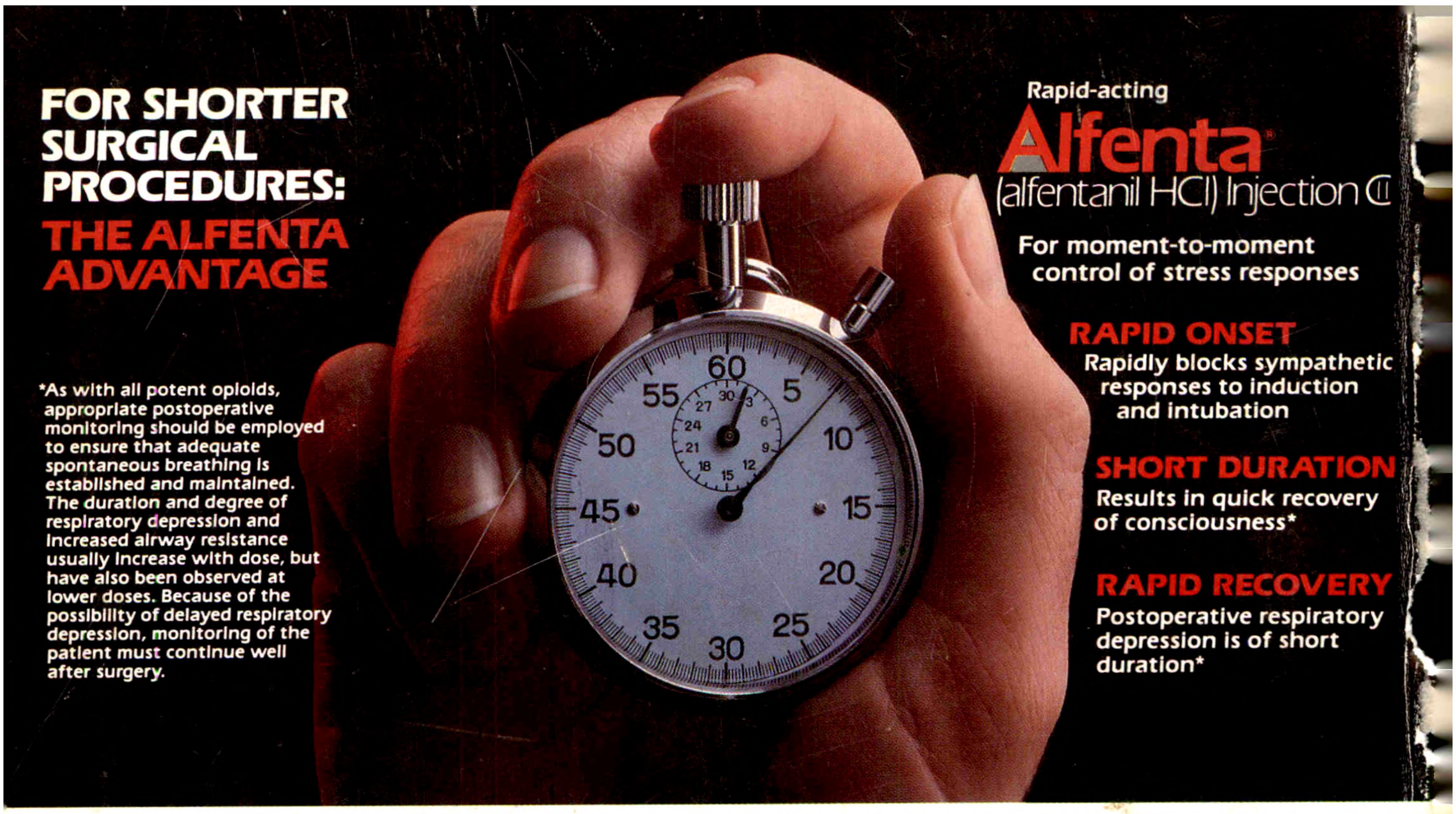
Francisco Convention and Visitor's Bureau Photo by Kerrick James.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For moment-to-moment control of stress responses
RAPID ONSET
Rapidly blocks sympathetic responses to induction and intubation
SHORT DURATION
Results in quick recovery of consciousness*
RAPID RECOVERY
Postoperative respiratory depression is of short duration*

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 μg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. for

JANSSEN
PHARMACEUTICA
Piscataway, N.J. 08854

March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

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